(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 561 639 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **93302064.6**

(51) Int. Cl.[5] : **C07K 7/56**, A61K 37/02

(22) Date of filing : **18.03.93**

(30) Priority : **19.03.92 US 854117**
16.12.92 US 992390

(43) Date of publication of application :
22.09.93 Bulletin 93/38

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

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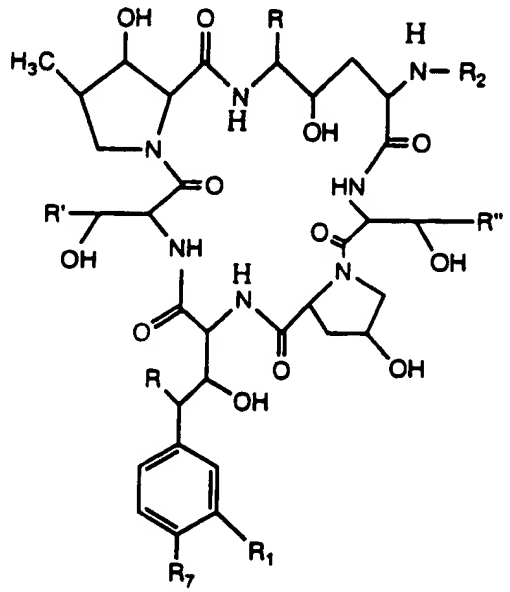
(54) Cyclic peptide antifungal agents and process for preparation thereof.

(57) Provided are compounds of the formula (1) :



(1)

wherein R' is hydrogen, methyl or $NH_2C(O)CH_2$- ;
R" is methyl or hydrogen ;
R is hydroxy or hydrogen ;
R_1 is hydroxy, hydrogen, or hydroxysulfonyloxy ;
R_7 is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonooxy ;
R_2 is a novel acyl side chain. Also provided are novel formulations, methods of inhibiting fungal and parasitic activity, and a process for preparing didehydroxy (R=H) forms of the compounds.

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Background of the Invention

This invention relates to cyclic peptide antifungal agents. In particular, it relates to acyl derivatives of the echinocandin class of cyclic peptide antifungal agents; to methods for treating antifungal and parasitic infections, and to formulations useful in the methods.

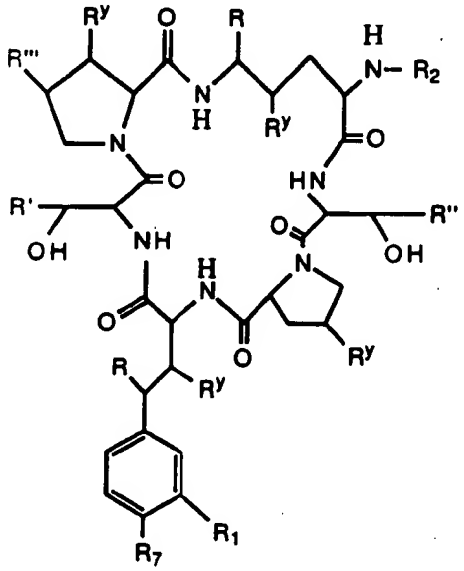
The compounds provided by this invention are semi-synthetic antifungal agents in that they are derived from the cyclic peptide antifungals which are produced by culturing various microorganisms. A number of cyclic peptide antifungals are known. Among these are echinocandin B (A30912A), aculeacin, mulundocandin, sporiofungin, L-671,329, FR901379, and S31794/F1. All such antifungals are structurally characterized by a cyclic hexapeptide core, or nucleus, the amino group of one of the cyclic amino acids bearing a fatty acid acyl group forming a side chain off the core or nucleus. For example, echinocandin B has a linoleoyl side chain while aculeacin has a palmitoyl side chain. These fatty acid side chains of the cyclic hexa- peptides can be removed by enzymatic deacylation to provide the free nucleus. (Formula (1), hereinafter, wherein R_2 is hydrogen.) Reacylation of the amino group of the nucleus provides semisynthetic antifungal compounds. For example, the echinocandin B nucleus provides a number of antifungal agents when reacylated with certain unnatural side chain moieties (see *Debono*, U.S. Pat. No. 4,293,489). Among such antifungal compounds is cilofungin which is represented by the formula (1) wherein R is methyl, R_1 is hydrogen and R_2 is p-(n-octyloxy)benzoyl.

Enzymatic deacylation of the cyclic hexapeptides is carried out with deacylase produced by the organism Actinoplanes utahensis and related microorganisms as described by *Abbott et al.*, U.S. Pat. No. 4,293,482.

The present invention provides acylated cyclic hexapeptides having unique side chain acyl groups which, inter alia impart enhanced antifungal and antiparasitic potency e.g. against pathogenic strains of Candida albicans. Also provided is a process for removing the aminal and benzylic hydroxy groups to result in a dideoxy compound of formula (1) (R = H).

Summary of the Invention

The compounds provided by this invention are represented by the following formula (1):



(1)

wherein

R' is hydrogen, methyl or $NH_2C(O)CH_2$-;

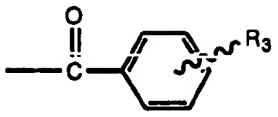
R" and R"' are independently methyl or hydrogen;

R and R^Y are independently hydroxy or hydrogen;

R_1 is hydroxy, hydrogen, or hydroxysulfonyloxy;

R_7 is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonooxy; and

I) R_2 is a substituted benzoyl group represented by the formula



wherein

A) R_3 is a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

B) R_3 is an unsaturated hydrocarbon group represented by the formula

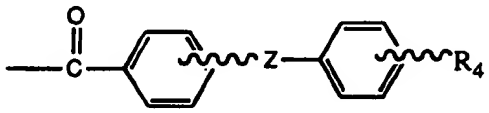
$$-Y-(C_1-C_{12}\ alkyl)$$

wherein Y is -C≡C- or -CH=CH-; or

C) R_3 is a group of the formula $-O-(CH_2)_m-G$, wherein m is as defined and G is C_7-C_{10} bicycloalkyl or C_7-C_{14} tricycloalkyl; or

D) R_3 is quinolyl; or

II) R_2 is an acyl group represented by the formula



wherein

Z is -O-, -C≡C-, -CH=CH-, $-CH_2-CH_2-$, $-CH_2-$, or a carbon to carbon bond;

A) R_4 is hydrogen, C_2-C_{12} alkynyl, C_2-C_{12} substituted alkynyl, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_1-C_{12} alkoxy, C_3-C_{12} cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

B) R_4 is phenyl substituted by amino, C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} substituted alkyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} substituted alkynyl, C_1-C_{12} alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined; or

C) R_4 is phenyl substituted with C_1-C_6 alkoxy substituted by fluoro, bromo, chloro or iodo; or

D) R_4 is C_1-C_{12} alkoxy substituted with C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_2-C_{12} alkynyl, amino, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, C_1-C_{12} alkanoylamino, phenyl substituted with a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-(O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined; or

E) R_4 is C_1-C_{12} alkoxy substituted with a group of the formula

wherein R_8 is C_1-C_6 alkoxy optionally substituted with phenyl; or

F) R_4 is a group represented by the formula

$$-O-(CH_2)_{p'}-W-R_5$$

wherein p' is an integer of from 2 to 4; W is pyrrolidino, pip ridin r piperazin , and R_5 is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycl alkyl, benzyl or C_3-C_{12} cycl alkylm thyl; or

G) R_4 is a group represented by the formula

$$-Y-R_6$$

wher in Y has the sam meanings defin d above; and

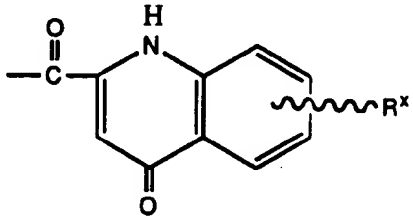
R_6 is C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl; C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, phenyl, C_3-C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, phenyl substituted by amin , C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, trifluoromethyl, -O-$(CH_2)p'$-W-R_5, or C_1-C_6 alkoxy substituted by fluoro, bromo, iodo or chloro; or

R_6 is a phenyl substituted by a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ \text{alkyl})$$

wherein m,n and p are as defined above; or

III) R_2 is a group having the formula

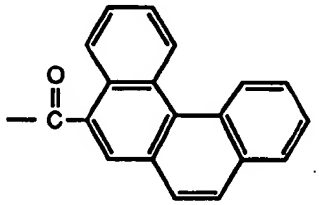


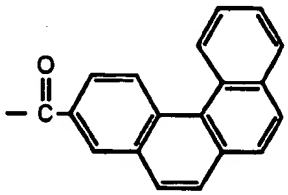
wherein R^x is C_1-C_{12} alkoxy or a polyoxa-alkyl group represented by the formula

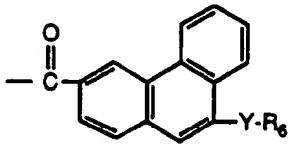
$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ \text{alkyl})$$

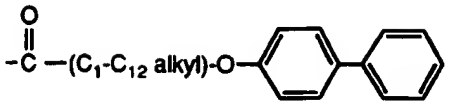
wherein m,n and p are as defined above; or

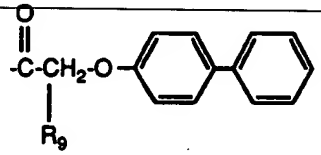
IV) R_2 is a group having the formula











wherein R_9 is phenyl, C_1-C_{12} alkyl, or C_1-C_{12} alkoxy; or

V) R_2 is naphthoyl substituted with R_4; and the pharmaceutically acceptable non-toxic salts thereof;

with the proviso that when

R' is methyl or $NH_2C(O)CH_2$-;

R" is methyl;

R'" is methyl;

R^Y is hydroxy;

R is hydroxy; and

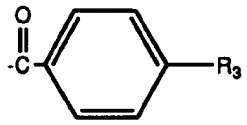
either a) or b):

a) R_1 is hydroxysulfonyloxy and R_7 is hydroxy, hydroxysulfonyloxy or phosphonooxy;

b) R_1 is hydrogen or hydroxysulfonyloxy and R_7 is hydroxysulfonyloxy or phosphonooxy;

R_2 is not

i)

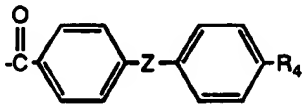


wherein R_3 is

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein p=O; nor

ii)



wherein Z is a carbon to carbon bond or -O- and R_4 is C_1-C_{12} alkoxy; nor

iii) naphthoyl substituted by R_4 wherein R_4 is hydrogen, phenyl, or C_1-C_{12} alkoxy.

Also provided are formulations and methods for inhibiting parasitic and fungal activity which employ the compounds of the invention, and a process for preparing the dideoxy form of the compounds.

Detailed Description

The term: "C_1-C_{12} alkyl" refers to the straight or branched chain alkyl hydrocarbon groups such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl groups; and the like.

The term "C_2-C_{12} alkenyl" refers to groups such as vinyl, 1-propene-2-yl, 1-butene-4-yl, 1-pentene-5-yl, 1-butene-1-yl, and the like.

The term "C_2-C_{12} alkynyl" refers t such gr ups as thynyl, propynyl, pentynyl, butynyl and the like.

The term "C_1-C_{12} alkylthio" ref rs to such groups as m thylthio, thylthio, t-butylthio, and th like.

The term "C_1-C_{12} alkoxy" refers to the straight r branched chain oxyalkyl groups such as, .g. meth xy, eth xy, propoxy, butoxy, heptoxy, octyloxy, dodecyl xy, and the like.

The term C_3-C_{12} cycloalkoxy" refers to such groups as cyclopropoxy, cyclobutoxy and the like.

The term "C_3-C_{12} cycloalkenyl" refers to such groups as cyclopropenyl, cyclobutenyl, cyclopentenyl, and the like.

The term "C_1-C_{12} substituted alkyl," "C_2-C_{12} substituted alkenyl", and "C_2-C_{12} substituted alkynyl", denotes the above substituted one or two times with halogen, hydroxy, protected hydroxy, amino, protected amino, C_1-C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, methylsulfonylamino, phenyl, substituted phenyl, or C_1-C_{12} alkoxy.

The term "substituted phenyl" is represented by a phenyl group substituted with one, two, or three moieties chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, carboxy, protected carboxy, carboxymethyl, hydroxymethoyl, amino, aminomethyl trifluoromethyl or N-(methylsulfonylamino)

The term "C_3-C_{12} cycloalkyl" refers to such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "C_1-C_4 alkylamino" refers to such groups as methylamino, ethylamino, n-butylamino and the like.

The term "di-(C_1-C_4 alkyl)amino" refers to such groups as dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methylethylamino, methyl-n-butylamino, and like tertiary amino groups.

The term "C_1-C_{12} alkanoylamino" refers to such groups as acylamino groups derived from the C_1-C_{12} carboxylic acids and are exemplified by formamido, acetylamino, propionylamino, butyrylamino, and the like.

The term "C_3-C_{12} cycloalkylmethyl" refers to those C_3-C_7 cycloalkyls described above further substituted by methyl.

The terms "C_7-C_{10} bicycloalkyl" and "C_7-C_{14} tricycloalkyl" refer to such groups as bicyclo[2.2.1.]hept-2-yl, bicyclo[2.2.1.]hep-4-en-2-yl, bicyclo[3.3.1.]nona-3-yl, bicyclo[3.3.1.]nona-2-yl, bicyclo[3.2.1.]oct-2-yl, bicyclo[2.2.2.]oct-2-yl, bicyclo[2.2.2]oct-5-en-2-yl, adamantyl and the like.

The term "dideoxy" refers to compounds of the formula (1) wherein R=H.

The term "inhibiting", such as used in relation to the methods for inhibiting parasitic and fungal activity, is defined to mean its normal definition, i.e., to stop, retard or prophylactically hinder or prevent.

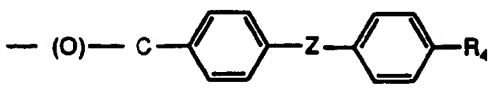
The term "activity", as used in relation to parasitic and fungal activity, includes growth thereof and attending characteristics and results from the existence of the parasite or fungus.

The term "contacting", as used in relation to the methods for inhibiting parasitic and fungal activity by contacting a compound of the invention with a parasite or fungus, is defined to mean its normal definition. However, the term does not imply any further limitations to the process, such as by mechanism of inhibition, and the methods are defined to encompass the spirit of the invention, which is to inhibit parasitic and fungal activity by the action of the compounds and their inherent anti-parasitic and anti-fungal properties, or in other words, the compounds, used in the method are the causative agent for such inhibition.

Examples of acyl groups represented by R_2 in formula (1) are benzoyl substituted by polyoxa-alkyl groups such as, e.g., 2-methoxyethoxy (p=0, m=1), 2-ethoxyethoxy, 2-(2-ethoxyethoxy)ethoxy (m=2, p=1, n=2), 3-(2-ethoxyethoxy)-propoxy, 3-(2-methoxyethoxy)butoxy, and like groups.

Examples of R_3 groups wherein R_2 is benzoyl substituted by an unsaturated hydrocarbon groups -Y-(C_1-C_{12}-alkyl) include e.g., acetylenic groups -C≡C-(C_1-C_{12} alkyl) and -CH_2=CH_2-(C_1-C_{12} alkyl) which may be cis- or trans- e.g. propenyl, butenyl, hexenyl, decenyl, and the like; propynyl, butynyl, hexynyl, undecynyl, and like alkynes.

Examples of acyl groups wherein R_2 is a group represented by the formula



are diphenyl ethers (Z=-0-), diphenyl acetylenes (Z=-C≡C-), stilbenes (Z=-CH=CH-), and biphenyls (Z = a carbon to carbon bond). Among examples of such biphenyl groups, wherein Z is a carbon to carbon bond i.e. a phenyl to phenyl bond, are 4-[4-(butyloxy)phenyl]benzoyl, 4-[4-(cycl butylmethoxy)-ph nyl]b nzoyl, 4-[4-cyclopentylmethoxy)phenyl]benzoyl, 4-[4-(cycl hexyleth xy)ph nyl]benzoyl, 4-[4-(n-hexyloxy)-ph nyl]benz yl, 4-phenylbenzoyl, 4-[4-(11-amin -undecyl xy)-phenyl]benz yl, 4-[4-(11-formamid und cyloxy)ph nyl]benzoyl, 4-[4-(is pentyloxy)phenyl]b nzoyl, and the like. Examples of such diphenyl ether acyl groups R_2 of the formula ab v wherein Z is an oxyg n atom ar 4-(4-butyloxyphen xy)benzoyl, 4-(4-h xyloxyph n xy)b n-

zoyl, 4-(4- thoxyphenoxy)benzoyl, 4-(4-benzyloxyph noxy)benzoyl, 4-[4-(3-chlorobutyloxy)phen xy]-benzoyl, 4-(4-dod cyloxyphenoxy)b nzoyl, 4-[4-(3-dim thylaminopropoxy)phenoxy]b nzoyl and the like. Examples of diphenylacetylene and stilbene acyl groups, R_2, wherein Z is an acetylenic bond or an ethylene bond are 4-styrylb nzoyl, 4-(4-meth xystyryl)b nzoyl, 4-(4-butyloxystyryl)b nz yl, 4-(phenylethynyl)b nzoyl, 4-(4-ethoxyphenylethynyl)benzoyl, 4-(4-cyclohexyloxyphenylethynyl)benzoyl, and the like. Examples of R_2 acyl groups represented by the foregoing formula wherein Z is a carbon to carbon bond and R_4 is represented by the formula $-O-(CH_2)_p-W-R_5$ are 4-[4-[2-(N-cyclohexylpiperidine-4-yl)ethoxy]phenyl]benzoyl, 4-[4-[2-(N-hexylpiperidine-4- yl)ethoxy]phenyl]benzoyl, 4-[4-[2-(4-benzylpiperidino)ethoxy]phenyl]benzoyl, 4-[4-[2-(4-cyclohexylpiperidino)- ethoxy]phenyl]benzoyl and like diphenyl acyl groups. Examples of such acyl groups wherein R_4 is represented by the formula $-Y-R_6$ include 4-[4-(phenylethynyl)phenyl]benzoyl, 4-[4-(phenylethynyl)phenoxy]benzoyl, 4-[4-(hexynyl)phenyl]benzoyl, 4-[4-(styryl)phenoxy]benzoyl, 4-[4-(4-benzylphenylethynyl)-phenyl]benzoyl, 4-[4-[4-4-methylpiperidino)ethoxy]phenylethynyl]phenyl]benzoyl and like acyl groups. Such acyl groups wherein R_4 is represented by the formula $-O-(CH_2)_p-W-R_5$ form salts of the basic amino groups of the piperidine and piperazine heterocyclic groups with both organic and inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid and with organic acids such as the sulfonic acids, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, acetic acid, chloroacetic acid, trifluoroacetic acid, benzoic acid, isophthalic acid, salicylic acid, citric acid, malic acid, succinic acid, malonic acid and like acids.

The following tables contain further examples of the cyclic peptides represented by the formula (1). Table 1 contains examples of cyclic peptides wherein the acyl group R_2 is of the formula

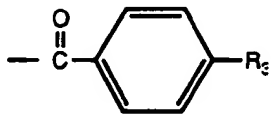
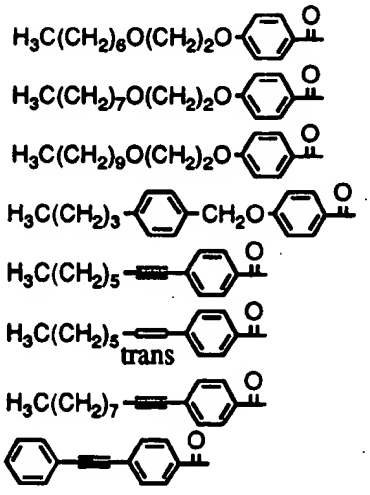


Table 1

R_2



The following Table 2 illustrat s the compound of the formula (1) wherein R_2 is represented by the formula

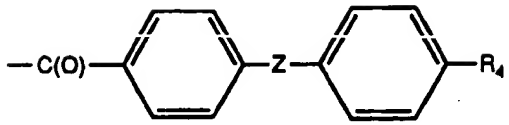

—C(O)—
Z
R4

Table 2

R_2

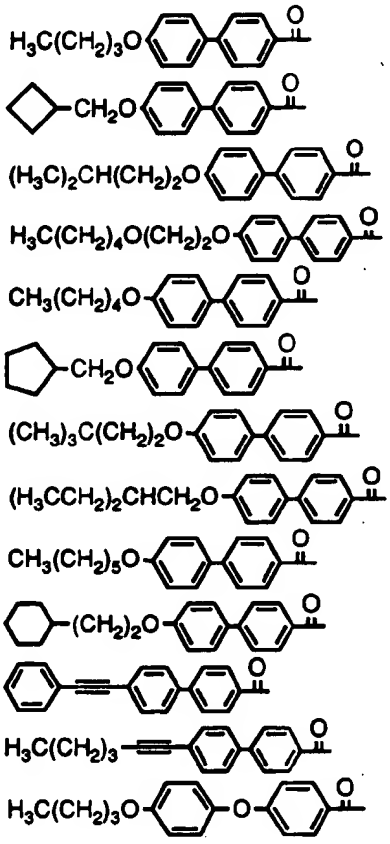
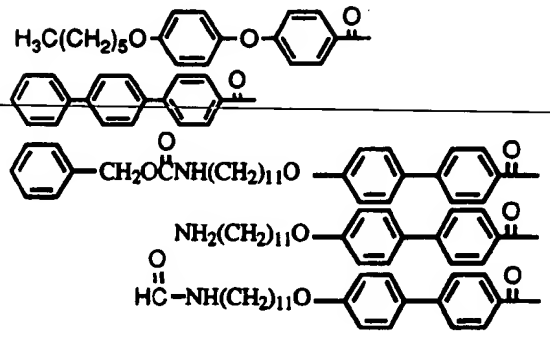

H3C(CH2)3O
CH2O
(H3C)2CH(CH2)2O
H3C(CH2)4O(CH2)2O
CH3(CH2)4O
CH2O
(CH3)3C(CH2)2O
(H3CCH2)2CHCH2O
CH3(CH2)5O
(CH2)2O
H3C(CH2)3
H3C(CH2)3O
O

Table 2 continued

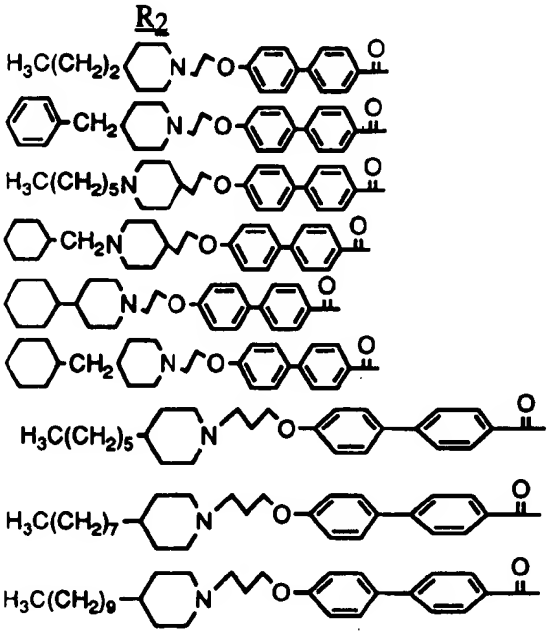
R_2



The following Table 3 illustrates compounds of formula 1 wherein R_2 is of the formula as indicated from Table 2 and R_4 is represented by the formula $-O-(CH_2)_p-W-R_5$.

Table 3

R_2



The acyl cyclohexapeptides represented by formula (1) exhibit antiparasitic activity, for example, they are especially active against the infectious fungi Candida albicans and Candida parapsilosis. They also exhibit significant activity against Aspergillus fumigatus. They are active both in vitro and in vivo and accordingly are useful in combating systemic fungal infections.

The compounds of the invention also inhibit the growth of certain organisms primarily responsible for opportunistic infections in immunosuppressed individuals. For example the compounds of the invention inhibit the growth of Pneumocystis carinii the causative organism of pneumocystis pneumonia in AIDS sufferers.

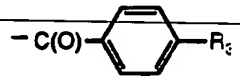
The antifungal activity of the compounds of the invention is determined in vitro in standard agar dilution tests and disc-diffusion tests wherein minimum inhibitory concentrations of the test compounds obtained. Stan-

dard in vivo tests in mice are used to determine the effective dose of the test compounds in controlling systemic fungal infections.

Tables 4A-E below contain the minimum inhibitory concentrations (MIC) in micrograms per milliliter (mcg/ml) for compounds of the invention against Candida albicans and Candida parapsilosis, and for certain compounds, the effective dose, ED_{50}, in mice.

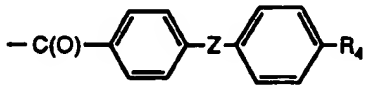
In Tables 4A-E, R'=CH_3, R''=CH_3, R'''=CH_3, R^Y=OH, R_7=OH and R_1=H, In Tables 4A-D, R=OH, while in Table E, R=H.

In the Table 4A, R_2 is of the formula



with R_3 being as indicated in the Table 4.

In Table 4B, R_2 is of the formula



where Z is -O- and R_4 is as indicated.

Table 4C is as Table 4B, except Z is a carbon-carbon bond.

Table 4D indicates compound activities in which R_2 is as defined.

In Table 4E, dideoxy (where R=H) compounds are illustrated with R_2 as indicated.

TABLE 4A

	MIC (mcg/ml)		ED_{50} (mg/kg)
R_3	C.alb.	C.parap.	
$-O(CH_2)_2-O-(CH_2)_2-O-C_2H_5$	>20	40	-
$-O-(CH_2)_2-O-C_5H_{11}$	>20	40	-
$-O-(CH_2)_2-OC_7H_{15}$	10	40	30.3
$-O-(CH_2)_2-O-C_8H_{17}$	2.5	80	4.4
$-O-(CH_2)_2-O-C_{10}H_{21}$	0.625	5	9.5
$-C\equiv C-C_5H_{11}$	2.5	29	10.5
$-CH=CH-C_6H_{13}$ (trans)	0.312	20	4.4
$-C\equiv C-C_8H_{17}$	0.156	10	-

TABLE 4B

	MIC (mcg/ml)		ED_{50} (mg/kg)
R_4	C.alb.	C.parap.	
$-O-C_4H_9$	>20	40	-
$-O-C_6H_{13}$	1.25	>20	22.9

TABLE 4C

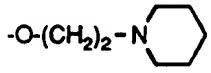
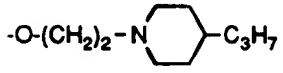
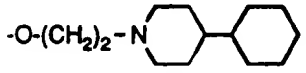
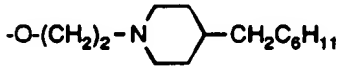
R_4	MIC (mcg/ml) C.alb.	C.parap.	ED_{50} (mg/ml)
$-O-C_4H_9$	0.78	10	0.84
$-O-CH_2$-cyclobutyl	0.312	10	2.50
$-O-CH_2$-cyclopentyl	0.039	2.5	1.20
$-O-C_5H_{11}$	0.156	0.625	1.86
$-O-C_6H_{13}$	0.039	1.25	1.10
$-O-CH_2CH_2$-cyclohexyl	0.039	20	1.6
$-O-CH_2-CH(C_2H_5)-C_2H_5$	0.039	2.5	4.6
$-O-CH_2-CH_2-CH(CH_3)_2$	0.309	5	2.00
$-O-CH_2-CH_2-C(CH_3)_3$	0.039	2.5	2.21
$-O-(CH_2)_2-O-C_5H_{11}$	1.25	20	0.60
$-C\equiv C-C_4H_9$	0.039	2.5	1.20
$-C\equiv C-C_6H_5$	0.039	0.625	0.60
$-C_6H_5$	0.078	10	1.3
$-O-(CH_2)_2-N(CH_3)_2$	>20	>20	-
	>20	>20	-
	5	>20	3.0
	0.312	40	0.64
	0.039	5	0.24

TABLE 4D

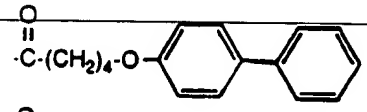
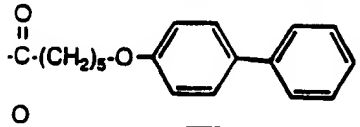
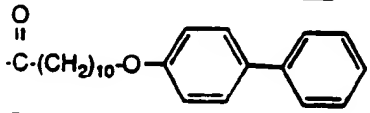
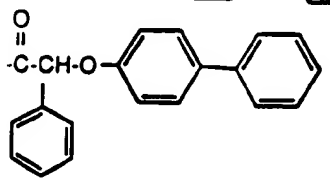
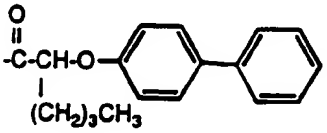
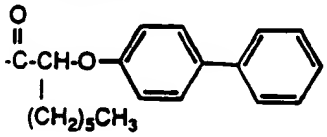
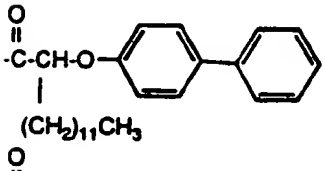
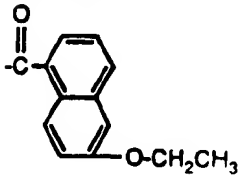
R_2	MIC (mcg/ml) C.alb.	C. parap.
	40	>80
	1.25	80
	0.0039	2.5
	5	>80
	80	>80
	80	>80
	10	>80
	>80	>80

TABLE 4D continued

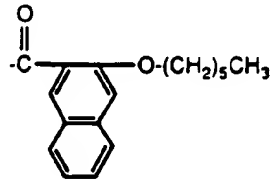
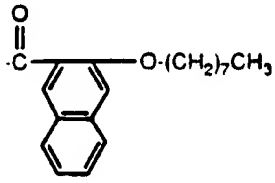
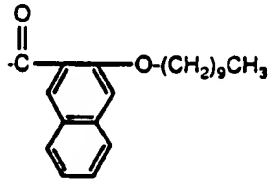
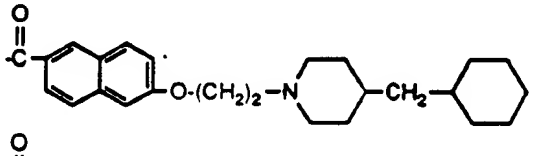
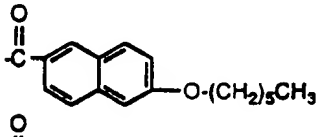
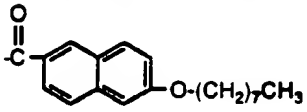
R_2	MIC (mcg/ml) C.alb.	C. parap.
	20	>80
	10	>80
	20	>80
	20	>80
	0.039	5
	0.078	0.312

TABLE 4D continued

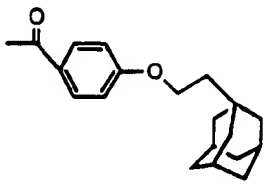
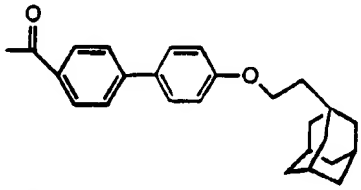
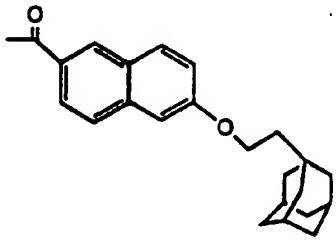
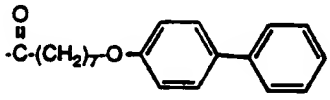
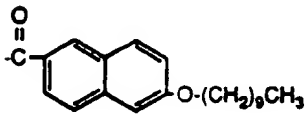
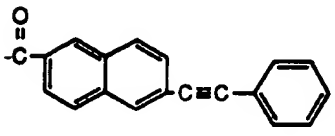
R_2	MIC (mcg/ml) C.alb.	C. parap.
	0.5	80
	0.005	0.156
	0.039	0.156
	0.156	20
	0.005	0.312
	0.312	5

TABLE 4D continued

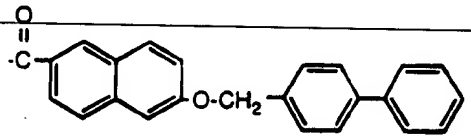
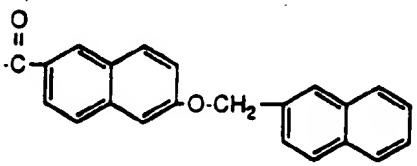
R_2	MIC (mcg/ml) C.alb.	C. parap.
	0.312	>80
	0.078	>20

TABLE 4E

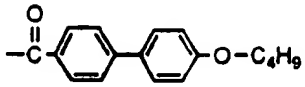
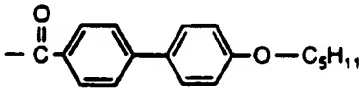
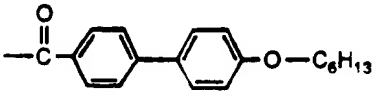
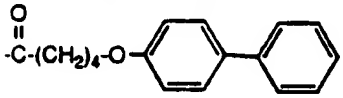
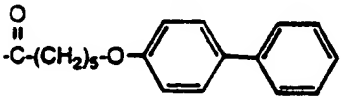
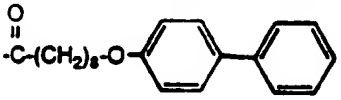
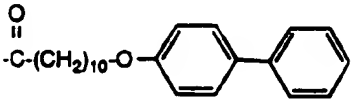
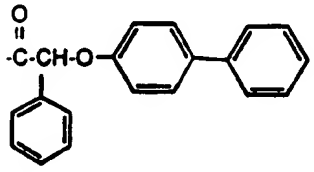
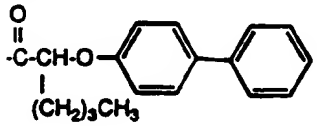
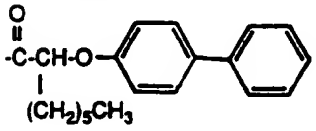
R_2	MIC (mcg/ml) C. alb.	C. parap.
	0.039	5.0
	>20	1.25
	0.039	2.5
	>80	>80
	1.25	40
	0.005	2.5
	0.0098	0.625
	80	>80
	20	>80
	40	>80

TABLE 4E continued

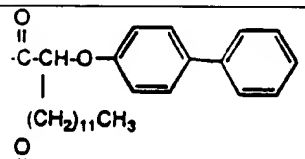
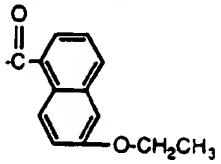
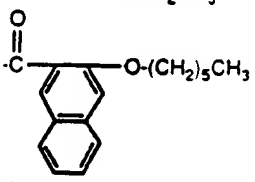
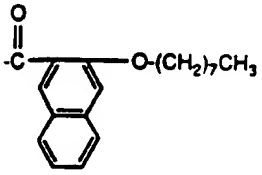
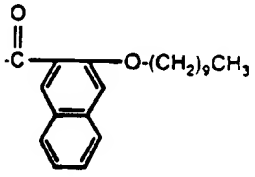
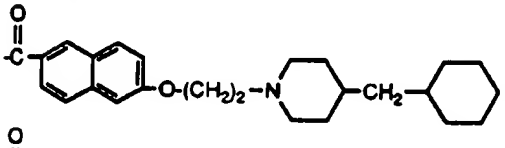
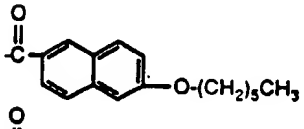
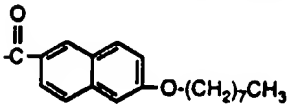
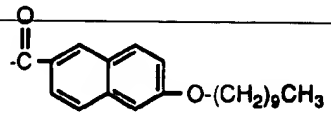
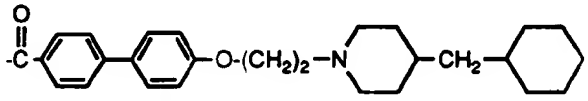
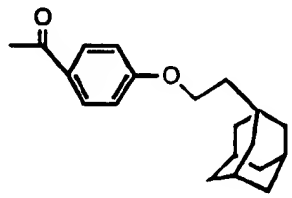
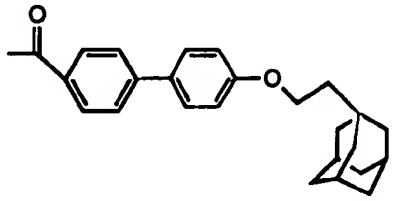
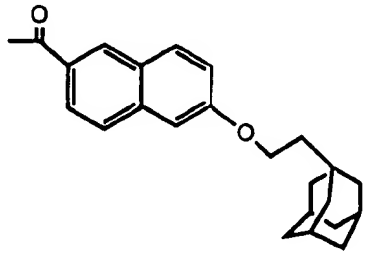
R_2	MIC (mcg/ml) C.alb.	C. parap.
	1.25	>80
	>80	>80
	10	>80
	10	>80
	5.0	>80
	1.25	>80
	0.078	1.25
	0.039	0.125

TABLE 4E continued

R_2	MIC (mcg/ml) C.alb.	C. parap.
	0.156	0.625
	0.156	5.0
	0.625	80
	0.005	0.156
	0.039	0.156

The non-dideoxy compounds of the invention (formula (1) are prepared with the amino nuclei of the cyclic hexapeptides which are represented by the formula when R_2 is hydrogen. These amino nuclei are obtained from the known natural products by the known enzymatic deacylation by which the fatty acid side chains of the natural compounds are removed. For example, echinocandin B which can be represented by the formula (1) wherein R'=R"=R'"= methyl, R is OH, R^Y is hydroxy, R_1 is H, R_7 is OH, and R_2 is linoleoyl, is deacylated to provide the echinocandin B nucleus (R_2=H) with the deacylase produced by the organism Actinoplanes utahensis as described by U.S. Patent Nos. 4,293,482 and 4,304,716.

The known natural cyclic hexapeptides which are N-deacylated to provide the amino nuclei starting materials include echinocandin B (also known as A-30912A), aculeacin (palmitoyl side chain), tetrahydoechinocandin B (stearoyl side chain), mulundocandin (branched C_{15} side chain), L-671,329 (C_{16} branched side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C_{15} branched side chain) and FR901379 (palmitoyl side chain). The amino nuclei obtained by the N-deacylation are then acylated by employing known amino acylation procedures to provide the N-acyl cyclic hexapeptides represented by the formula (1) wherein R_2 represents the acyl groups defined hereinabove. The acylating moiety is preferably an active ester of the carboxylic acid RCOOH such as the 2,4,5-trichlorophenyl ester. The R_2COOH precursor acids are prepared by the hydrolysis of the nitrile R_2CN or the ester R_2COOC_1-C_4 alk. These nitrile and ester intermediates are prepared by kn wn

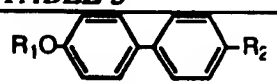
m thods.

The alk xy aromatic (ie. phenyl and biphenyl) compounds of Tables 5-10 are prepared by one of the tw following pr cedures:

A. The hydroxyaromatic compound (1 equivalent) is dissolved in ac tonitrile (200-300 ml) and a base, such as potassium t-butoxide or potassium carbonate, (1-equivalent), is added. An alkyl bromide, iodide, or p-toluenesulfonate (1 equivalent) is then added and the solution is refluxed for 6 hours. The solvent is evaporated in vacuo and the residue is dissolved in ether and 2N sodium hydroxide. The ether layer is dried over magnesium sulfate and evaporated to give the alkoxyaromatic product.

B. The hydroxyaromatic compound (1 equivalent), alkyl alcohol (1 equivalent), and triphenylphosphine (1 equivalent) are dissolved in tetrahydrofuran (200-300 ml) and diethylazodicarboxylate (1 equivalent) is added dropwise over 10 minutes at room temperature. After 17 hours the solvent is removed in vacuo and the residue is dissolved in ether. This organic layer is extracted with 2N sodium hydroxide solution, dried over magnesium sulfate, and evaporated to give a product which is crystallized from ether/pentane or, if the product contains a tertiary amine, the hydrochloride salt is formed and crystallized from methanol/ethyl acetate.

TABLE 5



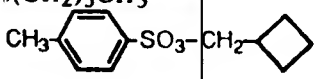
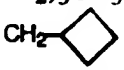
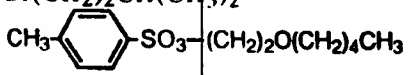
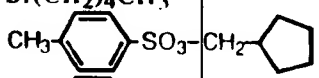
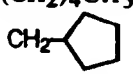
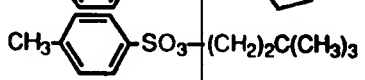
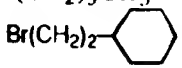
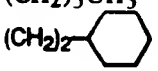
Alkyl halide or tosylate	Wt. g	Method	R_1	R_2	Wt. g
$I(CH_2)_3CH_3$	9.4	A	$-(CH_2)_3CH_3$	CN	3.2
	12.3	A		CN	5.3
$Br(CH_2)_2CH(CH_3)_2$	7.7	A	$-(CH_2)_2CH(CH_3)_2$	CN	9.2
	7.6	A	$(CH_2)_2O(CH_2)_4CH_3$	CN	4.8
$Br(CH_2)_4CH_3$	15.3	A	$-(CH_2)_4CH_3$	CN	20.3
	13.0	A		CN	12.2
	13.1	A	$(CH_2)_2C(CH_3)_3$	CN	11.8
$BrCH_2CH(CH_2CH_3)_2$	8.5	A	$-CH_2CH(CH_2CH_3)_2$	CN	3.0
$I(CH_2)_5CH_3$	10.8	A	$-(CH_2)_5CH_3$	CN	11.4
	4.2	A		CO_2CH_3	4.5

TABLE 6

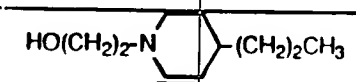
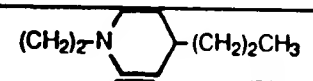
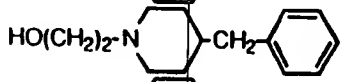
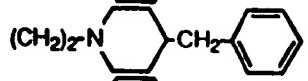
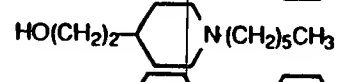
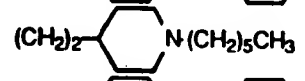
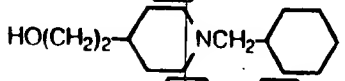
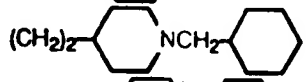
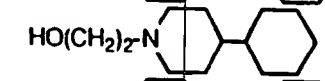
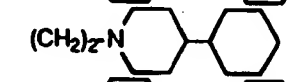
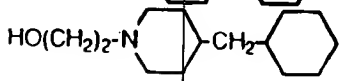
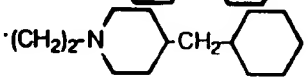
Alcohol	wt. g	Method	R	wt. g
	3.6	B		6.2
	6.1	B		4.3
	0.5	B		0.8
	0.5	B		0.5
	2.3	B		1.3
	9.3	B		9.6

TABLE 7

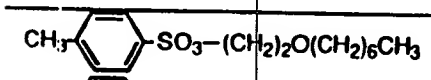
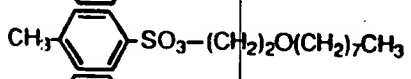
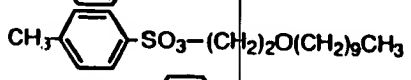
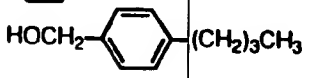
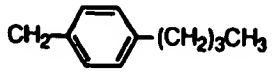
Tosylate or alcohol	wt. g	Method	R	wt. g
	23.4	A	$-(CH_2)_2O(CH_2)_6CH_3$	20.9
	25.8	A	$-(CH_2)_2O(CH_2)_7CH_3$	7.9
	27.1	A	$-(CH_2)_2O(CH_2)_9CH_3$	21.0
	10.0	B		13.6

TABLE 8

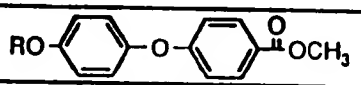
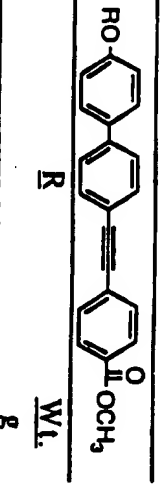
Alkyl halide	wt. g	Method		wt. g
$I(CH_2)_3CH_3$	6.1	A	$-(CH_2)_3CH_3$	12.3
$I(CH_2)_5CH_3$	4.3	A	$-(CH_2)_5CH_3$	4.7

Table 9



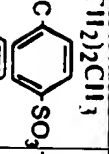
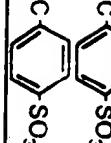
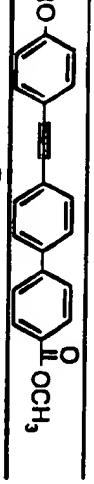
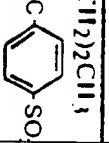
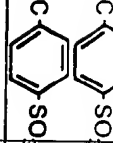
Alkylhalide or tosylate	Wt.	Method	R	Wt.
	g			g
$I(CH_2)_2CH_3$	2.6	A	$-(CH_2)_2CH_3$	4.4
H_3C  $SO_3-(CH_2)_2O(CH_2)_3CH_3$	2.7	A	$-(CH_2)_2O(CH_2)_3CH_3$	2.6
H_3C  $SO_3-(CH_2)_2OC(CH_3)_3$	2.7	A	$-(CH_2)_2OC(CH_3)_3$	2.6

Table 10



Alkylhalide or tosylate	Wt.	Method	R	Wt.
	g			g
$I(CH_2)_2CH_3$	3.8	A	$-(CH_2)_2CH_3$	1.4
H_3C  $SO_3-(CH_2)_2O(CH_2)_3CH_3$	3.6	A	$-(CH_2)_2O(CH_2)_3CH_3$	5.1
H_3C  $SO_3-(CH_2)_2OC(CH_3)_3$	4.9	A	$-(CH_2)_2OC(CH_3)_3$	5.2

The alkynyl and alkenyl aromatic compounds contained in Tables 11-14 are prepared by the following procedure:

An aromatic bromide, iodide, or trifluoromethane-sulfonate (1 equivalent) is dissolved in acetonitrile (600 ml/0.1 mole of aromatic reactant) under a nitrogen atmosphere. An alkyne or alkene (1 equivalent), triethylamine (2 equivalents), palladium dichloride (0.05 equivalents), triphenylphosphine (0.1 equivalents), and cuprous iodide (0.025 equivalents) are added and the solution is refluxed for 17 hours. The solvent is removed in vacuo and the residue is slurried in ether (300 ml). Solids are removed by filtration and the filtrate is washed with 1N hydrochloric acid solution. The organic layer is dried over magnesium sulfate and vaporated to yield the product.

TABLE 11

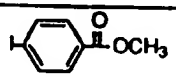
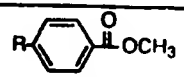
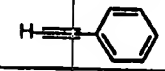
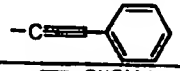
Acetylene or olefin	wt. g	 wt. g	 R	wt. g
H-≡-$(CH_2)_5CH_3$	12.1	28.8	-C≡-$(CH_2)_5CH_3$	26.2
H-=-$(CH_2)_5CH_3$	6.1	14.4	-CH=-$(CH_2)_5CH_3$ (trans)	0.6
H-≡-$(CH_2)_7CH_3$	15.2	28.8	-C≡-$(CH_2)_7CH_3$	28.1
	1.9	5.1		1.9
H-≡-$Si(CH_3)_3$	4.3	11.5	-≡-$Si(CH_3)_3$	11.2

TABLE 12

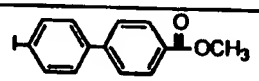
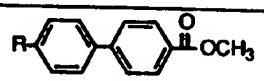
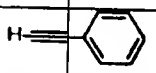
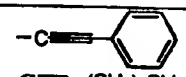
Acetylene	wt. g	 wt. g	 R	wt. g
	1.8	6.0		2.6
H-≡-$(CH_2)_3CH_3$	1.4	6.0	-C≡-$(CH_2)_3CH_3$	5.1
H-≡-$Si(CH_3)_3$	10.9	40.0	-≡-$Si(CH_3)_3$	23.3

TABLE 13

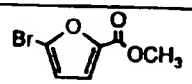
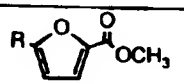
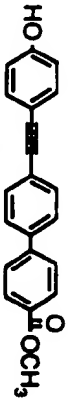
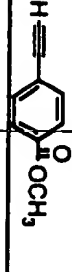
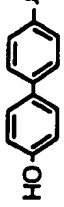
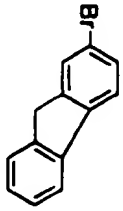
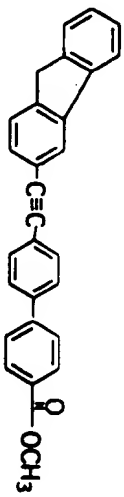
Acetylene	wt. g	 wt. g	 R	wt. g
H-≡-$(CH_2)_7CH_3$	7.6	11.3	-C≡-$(CH_2)_7CH_3$	11.4

TABLE 14

Acetylene	wt. g	Halide	wt. g	Product	wt. g
	10.5		9.7		10.2
	22.2		34.4		19.4
	1.2		1.2		1.5

The aromatic boronic acids list d in Table 15 were prepared by the foll wing procedur :

An aromatic halide (1 equivalent) is cool d to -78°C in tetrahydrofuran solvent. Butyl lithium (1.2 equivalents) is added. After 15 min triisopropyl borate (2 equivalents) is added and after 10 min of stirring the cooling bath is removed. When the reaction has warmed to room temperature wat r is added to quench the reaction followed by 1N HCl. The organic lay r is rem ved under reduced pr ssure l aving a solid precipitate which is collected by filtration. This solid is washed with hexane leaving the pure boronic acid.

The terphenyl esters listed in Table 16 were made in the following manner:

An aromatic boronic acid (1 equivalent), methyl 4-iodobenzoate (1 equivalent), and potassium carbonate (1.5 equivalents) were mixed in a nitrogen-purged toluene solution. Alternatively, the trichloro phenyl ester of iodobenzoate my be used. Added tetrakis(triphenylphosphine)palladium (0.03 equivalents) and refluxed for 7 hrs. The solution was decanted to remove the potassium carbonate and reduced in vacuo. The residue was triturated with acetonitrile and the product solid was collected by filtration.

TABLE 15

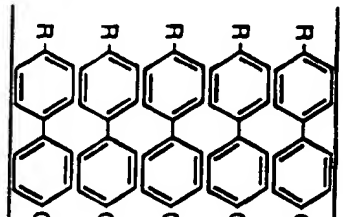
R	R=Br Wt. (g)	R=B(OH)$_2$ Wt. (g)
 $O(CH_2)_3CH_3$	10.6	6.1
$O(CH_2)_4CH_3$	31.0	12.0
$O(CH_2)_5CH_3$	10.9	4.1
$O(CH_2)_2O(CH_2)_3CH_3$	13.6	5.7
$O(CH_2)_2OC(CH_3)_3$	5.0	1.9

TABLE 16

R	$(HO)_2B$-R Wt. (g)	H_3CO-C(=O)-I Wt. (g)	H_3CO-C(=O)-R Wt. (g)
$-O(CH_2)_3CH_3$	5.0	3.2	4.2
$-O(CH_2)_4CH_3$	6.0	3.7	5.2
$-O(CH_2)_5CH_3$	3.4	2.8	3.5
$-O(CH_2)_2O(CH_2)_3CH_3$	3.7	3.6	3.7
$-O(CH_2)_2OC(CH_3)_3$	1.8	1.5	2.2

The aromatic nitriles or carboxylat esters described in Tabl s 5-16 can be convert d to carboxylic acids

by one of the two following hydrolysis procedures:

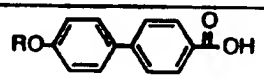
A. An aromatic nitrile is dissolved in ethanol and an excess of 50% sodium hydroxide solution and refluxed for 2 hours. Water is added until a solid precipitates. The precipitate is collected by filtration, added to dioxane and 6N hydrochloric acid solution and refluxed for 17 hours. Water is added and the carboxylic acid product crystallizes and is collected by filtration and dried under vacuum.

B. A carboxylate methyl ester is dissolved in methanol, excess 2N sodium hydroxide solution is added and the solution is refluxed for 5 hours. The solution is made acidic with excess hydrochloric acid and water is added until a precipitate forms. The carboxylic acid is collected by filtration and dried under vacuum.

The carboxylic acids are converted to 2,4,5-trichlorophenyl esters shown in Tables 17-25 by the following general procedure:

The aromatic acid (1 equivalent), 2,4,5-trichlorophenol (1 equivalent), and N,N'-dicyclohexylcarbodiimide (1 equivalent) are dissolved in methylene chloride. The mixture is stirred for 17 hours after which it is filtered. The filtrate is evaporated to dryness and the residue is dissolved in ether, filtered, and pentane is added until crystallization begins. The crystalline product is collected by filtration and dried under vacuum.

TABLE 17



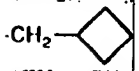
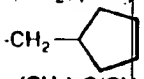
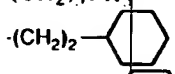
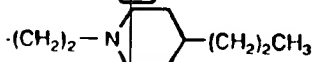
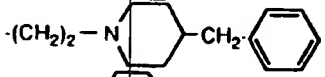
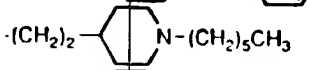
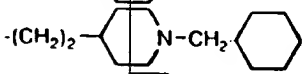
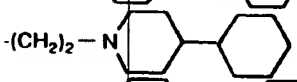
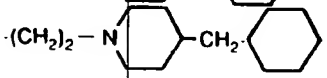
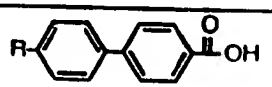
R	2,4,5-trichlorophenol ester wt. g	wt. g
$-(CH_2)_3CH_3$	1.9	1.8
	4.2	4.4
$-(CH_2)_2CH(CH_3)_2$	3.0	1.7
$-(CH_2)_2O(CH_2)_4CH_3$	2.2	1.3
$-(CH_2)_4CH_3$	5.7	5.1
	4.4	3.1
$-(CH_2)_2C(CH_3)_3$	2.3	2.6
$-CH_2CH(CH_2CH_3)_2$	1.5	0.8
$-(CH_2)_5CH_3$	5.3	4.8
	3.1	1.0
	3.3	1.5
	3.0	2.3
	1.0	1.0
	2.0	0.8
	7.2	0.8
	7.5	7.3

TABLE 18



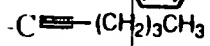
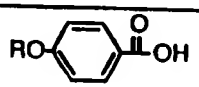
R	wt. g	2,4,5-trichlorophenol ester wt. g
	2.0	0.6
	1.1	0.6

TABLE 19



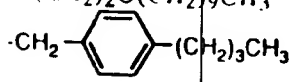
R	wt. g	2,4,5-trichlorophenol ester wt. g
$-(CH_2)_2O(CH_2)_6CH_3$	5.6	2.9
$-(CH_2)_2O(CH_2)_7CH_3$	7.8	6.6
$-(CH_2)_2O(CH_2)_9CH_3$	6.4	1.3
	4.0	3.2

TABLE 20

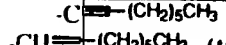
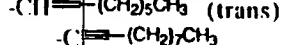
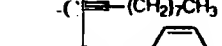
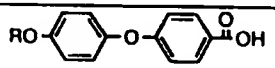
R	wt. g	2,4,5-trichlorophenol ester wt. g
	4.6	3.5
 (trans)	1.2	0.5
	11.1	13.2
	1.5	1.5

TABLE 21



R	wt. g	2,4,5-trichlorophenol ester wt. g
$-(CH_2)_3CH_3$	5.8	1.4
$-(CH_2)_5CH_3$	3.8	2.4

TABLE 22

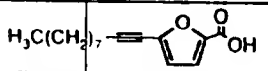
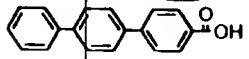
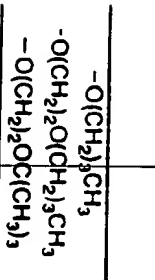
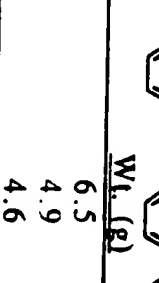
Carboxylic acid	wt. g	2,4,5-trichlorophenol ester wt. g
	8.3	13.2
	0.8	1.2

TABLE 23



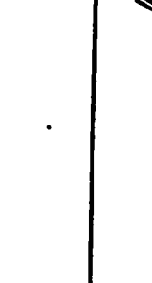
R	2,4,5-Trichlorophenol ester Wt. (g)
$-O(CH_2)_3CH_3$	3.3
$-O(CH_2)_4CH_3$	3.0
$-O(CH_2)_5CH_3$	2.3
$-O(CH_2)_2O(CH_2)_3CH_3$	3.3
$-O(CH_2)_2OC(CH_3)_3$	1.3

TABLE 24



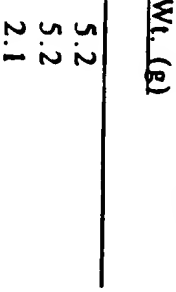
R	2,4,5-Trichlorophenol ester Wt. (g)
$-O(CH_2)_3CH_3$	6.5
$-O(CH_2)_2O(CH_2)_3CH_3$	4.9
$-O(CH_2)_2OC(CH_3)_3$	4.6

TABLE 25



R	2,4,5-Trichlorophenol ester Wt. (g)
$-O(CH_2)_3CH_3$	2.9
$-O(CH_2)_2O(CH_2)_3CH_3$	2.0
$-O(CH_2)_2OC(CH_3)_3$	2.0

TABLE 26



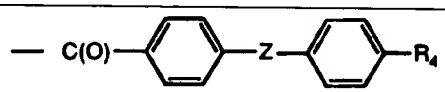
R	2,4,5-Trichlorophenol ester Wt. (g)
$-O(CH_2)_3CH_3$	2.5
$-O(CH_2)_2O(CH_2)_3CH_3$	1.5
$-O(CH_2)_2OC(CH_3)_3$	1.3

The dideoxy compounds of formula (1) are prepared by removing the benzylic and aminal hydroxy groups. The process includes subjecting a non-dideoxy compound of formula (1) (wherein R_2 may be hydrogen or acyl) to a strong acid such as trichloroacetic acid, trifluoroacetic acid or borontrifluoride etherate with trifluoroacetic acid being preferred, and a reducing agent, such as sodium cyanoborohydride or triethylsilane, with triethylsilane being preferred. The reaction takes place at temperatures from between -5 and 70°C, and in a suitable solvent such as methylene chloride, chloroform or acetic acid, with dichloromethane being preferred. The acid should be present in an amount of 2 to 60 moles per mole of substrate, and the reducing agent should be present in an amount of 2 to 60 moles per mole of substrate. This process affords selective removal of the aminal and

benzylic hydroxy groups.

The compounds represented by the formula (1) have improved properties over the previously known N-acyl hexapeptide antifungals. For example, in general the compounds exhibit oral bioavailability, a property which is important for any systemic antifungal agent. Also, numerous N-acyl compounds of the formula (1) have enhanced antifungal activity and enhanced water solubility.

Among the N-acyl hexapeptides represented by the formula (1) certain are preferred embodiments of the invention. The compounds wherein R_2 is a diphenyl acyl group



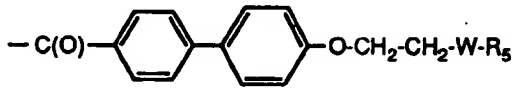
wherein Z is a carbon to carbon bond and R_4 is an alkoxy, cycloalkoxy or cycloalkylalkoxy group are preferred antifungals. Also preferred compounds are represented when Z is a carbon to carbon bond and R_4 is -Y-R_6 and R_6 is C_1-C_{12} alkyl phenyl or substituted phenyl and Y is an acetylenic bond.

A further preferred group of N-acyl hexapeptides is represented when Z is a carbon to carbon bond and R_4 is represented by -O-$(CH_2)_p$-W-R_5 and wherein W is a piperidine group.

Examples of preferred compounds of the above first mentioned group include 4-(4-alkoxyphenyl)benzoyl wherein the alkoxy group is preferably a C_5-C_{10} alkoxy group or C_1-C_4 alkoxy substituted by C_3-C_7 alkyl. Examples of such preferred compounds are represented by the formula 1 wherein R_2 is 4-(4-n-hexyloxyphenyl)benzoyl, 4-(4-n-heptyloxyphenyl)benzoyl, 4-(4-n-octyloxyphenyl)benzoyl, 4-[4-(3,3-dimethylbutoxy)phenyl]benzoyl, 4-[4-(2-cyclopentyl-ethoxy)phenyl]benzoyl and 4-[4-(2-cyclohexyloxyethoxy)phenyl]benzoyl.

Examples of the second above mentioned preferred compounds wherein R_4 is -Y-R_6 include 4-[4-(phenylethynyl)phenyl]benzoyl and 4-[4-(n-butylethynyl)phenyl]benzoyl.

Examples of preferred compounds of the invention wherein R_4 represents -O-$(CH_2)_p$-W-R_5 are represented when R_2 has the formula

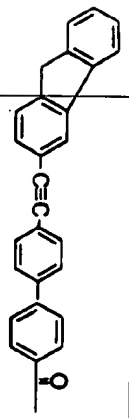


wherein W-R_5 is piperidino, 4-n-propylpiperidino, 4-benzylpiperidino, 4-cyclohexylpiperidino, 4-cyclohexylmethylpiperidino, and the pharmaceutically acceptable acid addition salts such as the hydrochloride salts, the sulfate salts or the phosphate salts.

Preferred cyclohexylpeptide compounds are represented by the formula 1 wherein R'=R"= methyl, R_1 is hydrogen and R_2 is a preferred acyl group as defined hereinabove.

Table 26 is a list of the most preferred R_2 substituents, wherein R=R_7=R^Y=OH; R'=R"= R'"=CH_3; and R_1=H.

TABLE 26

R_2	Ester Reactant (g)	A30912A Nucleus (g)	Product (g)	FABMS
$H_3C(CH_2)_2O$	5.2	6.9	1.4	1142.4951**
$(H_3C)_3CO(CH_2)_2O$	2.1	2.5	2.0	1200.5336**
$H_3C(CH_2)_3O(CH_2)_2O$	5.2	6.4	1.1	1194.5282*
$H_3C(CH_2)_2O$	2.4	3.3	0.9	1136.4832*
$H_3C(CH_2)_3O(CH_2)_2O$	2.0	3.2	3.0	1194.5213*
$(H_3C)_3CO(CH_2)_2O$	1.3	1.5	2.4	1194.5247*
$H_3C(CH_2)_3O$	4.6	7.4	1.3	1126.5025*
$H_3C(CH_2)_4O$	2.5	3.7	5.1	1140.5103*
$H_3C(CH_2)_5O$	3.5	5.0	1.4	1154.5343*
$H_3C(CH_2)_3O(CH_2)_2O$	4.4	6.7	6.5	1170.5234*
$(H_3C)_3CO(CH_2)_2O$	1.9	2.9	1.4	1170.5261*
	1.8	2.6	0.2	1166.4758*

* m+1; ** m+[Li]+

The N-acylhexapeptides provided by this invention are useful in the treatment of fungal inf ctions both systemic infections and skin inf ctions. Accordingly this invention also provides a method for treating fungal infections in man and animals which comprises administering to said host an antifungally ff ctive non-toxic amount of an N-acyl-cyclohexapeptide represented by the f rmula 1. A pref rred antifungal method comprises

administering an N-acylhexapeptid compound wher , in formula 1, R'=R"= methyl, R_1 is hydrog n and R_2 is a preferred acyl group as defin d hereinabove.

The antifungal compound can be administer d parenterally, e.g. i.m., i.p. or s.c., nasally, oraily or can b appli d topically for skin infecti ns. The dose administer d of cours will vary dep nding on such factors as the nature and severity of the infection, the age and general health of the host and the tolerance of a particular host to the particular antifungal agent. The particular dose regimen likewise may vary according to such factors and may be given in a single daily dose or in multiple doses during the day. The regimen may last from about 2-3 days up to about 2-3 weeks or longer.

This invention also provides pharmaceutical formulations useful for administering the antifungal compounds of the invention. These formulations comprise an N-acylhexapeptide represented by the formula 1 or a pharmaceutically acceptable, non-toxic salt thereof and a pharmaceutically acceptable carrier.

For parenteral administration the formulation comprises a compound of the formula 1 and a physiologically acceptable diluent such as deionized water, physiological saline, 5% dextrose and other commonly used diluents. The formulation may contain a solubilizing agent such as a polyethylene glycol or polypropylene glycol or other known solubilizing agent. Such formulations may be made up in sterile vials containing the antifungal and excipient in a dry powder or lyophilized powder form. Prior to use, the physiologically acceptable diluent is added and the solution withdrawn via syringe for administration to the patient. For oral administration, the antifungal compound is filled into gelatin capsules or formed into tablets. Such tablets also contain a binding agent, a dispersant or other suitable excipients suitable for preparing a proper size tablet for the dosage and particular antifungal compound of the formula 1. For pediatric or geriatric use the antifungal compound may be formulated into a flavored liquid suspension, solution or emulsion. A preferred oral carrier system is lineolic acid, cremophor RH-60 and water and preferably in the amount (by volume) of 8% lineolic acid, 5% cremophor RH-60, and 87% sterile water. The compound is added to the system in an amount of 2.5 to 40 mg/ml.

For topical use the antifungal compound can be formulated with a dry powder for application to the skin surface or it may be formulated in a liquid formulation comprising a solubilizing aqueous liquid or non-aqueous liquid, e.g., an alcohol or glycol. Such formulations are useful forms for use in the antifungal method provided herein.

The N-acylcyclohexapeptides provided herein may be formulated as described above in unit dosage formulations comprising for injection between about 50 mg and about 500 mg per vial. For oral use gelatin capsules or tablets comprising between about 100 mg and about 500 mg per capsule or tablet can be provided.

Preferred formulations of the invention comprises the active ingredient presented by the formula 1 wherein R'=R"= methyl, R_1 is hydrogen and R_2 is 4-[4-(phenylethynyl)-phenyl]benzoyl in gelatin capsules or as active ingredient the antifungal represented by the formula 1 wherein R'=R"= methyl, R_1 is hydrogen and R_2 is 4-[4-[2-(4-cyclohexyl-piperidino)ethoxy]phenyl]benzoyl or the hydrochloride salt form thereof in tablet or gelatin capsules. Further preferred formulations are those in which a preferred compound, as described above, is employed.

In yet a further aspect of the present invention there is provided a method for treating patients suffering from Pneumocystis pneumonia. The method can be used prophylactically to prevent the onset of the infection which is caused by the organism Pneumocystis carinii. The N-acylcyclicpeptide can be administered parenterally, e.g. via intramuscular (i.m), intravenous (iv.) or intraperitoneal (i.p.) injection, or orally or by inhalation directly into the airways of the lungs. Preferably the cyclic peptide is administered via inhalation of an aerosol spray formulation of the compound.

An effective amount of a cyclic peptide will be between about 3 mg/kg of patient body weight to about 100 mg/kg. The amount administered may be in a single daily dose or multiple doses e.g. two, three or four times daily throughout the treatment regimen. The amount of the individual doses, the route of delivery, the frequency of dosing and the term of therapy will vary according to such factors as the intensity and extent of infection, the age and general health of the patient, the response of the patient to therapy and how well the patient tolerates the drug. It is known that PCP infections in AIDS patients are highly refractory owing to the nature of the infection. For example, in severe, advanced infections the lumenal surface of the air passages becomes clogged with infectious matter and extensive parasite development occurs in lung tissue. A patient with an advanced infection will accordingly require higher doses for longer periods of time. In contrast, immune deficient patients who are not severely infected and who are susceptible to PCP can be treated with lower and less frequent prophylactic doses.

The activity f th cyclicpeptid represented by th formula 1 is demonstrated in immunosuppressed rats. The tests wer carried out in g neral as follows. One w ek after initiati n f immunosuppressi n rats w re inoculat d intratracheally with parasites and maintained n immunosuppression f r the remainder f th study. Prophylactic treatments began ne day aft r parasite inoculation and therapeutic treatm nts began 3 or 4 w eks lat r after mod rat PCP dev loped. Eight r ten animals were assigned t th f llowing groups: thos

receiving test compound; non-treated Pneumocystis infected control animals; animals treated with trimethoprim-sulfamethoxazole (TMP-SMX); or non-treated, non-infected control animals. The efficacy of different treatments was evaluated by monitoring animal weights and survival during the studies and by determining the severity of PCP at necropsy. Stained impression smears of the lungs and stained lung homogenates were evaluated to determine the intensity of P. carinii infection.

The immune deficient rats employed in the tests were prepared as follows. Female Lewis rats weighing from 120-140 g each were immune suppressed with methyl prednisolone acetate at a dose of 4 mg/100 g for the first week, 3 mg/100 g for the second week and continuing weekly thereafter at 2 mg/100 g. All rats, except for the non-infected control rats, were inoculated intratracheally with 0.1 ml to 0.2 ml of Dulbecco's Modified Eagle Media containing between $>10^5$ and 10^6 P. carinii (trophozoites, precysts and cysts) harvested from the lungs of heavily infected donor animals (infection scores of 6) and maintained as cryopreserved (liquid nitrogen) inocula. Rats were maintained on immune suppression and PCP was allowed to develop for 3 or 4 weeks before initiation of therapy with test compounds. Body weights were recorded weekly and rats were allocated into treatment groups such that each group had a similar distribution of percent weight loss among animals. Rats were treated with test compounds for 2 or 3 weeks and then were necropsied. For prophylaxis studies, administration of test compound was initiated one day after intratracheal inoculation of parasites and was continued until the rats were necropsied.

Following the evaluation period for test compounds, the rats were necropsied and test results evaluated by Giemsa-stained, silver-methenamine stained impression smears and/or by silver-methenamine stained lung homogenate (see below). Necropsy was carried out as follows. The test rats were anesthetized with a mixture of ketamine hydrochloride and xylazine and then exsanguinated via the right atrium. Internal organs in the abdominal and thoracic cavities were examined for gross lesions.

A small portion of lung tissue from the left lobe of each rat was used to make the impression smears described below. Giemsa-stained impression smears were evaluated to determine the total number of parasites (trophozoites, precysts, and cysts). Impression smears from rats in groups whose treatments exhibited some anti-Pneumocystis activity (as judged by infection scores from Giemsa-stained slides) and from rats in the control groups were also stained with methamine silver, a stain specific for the cyst wall of the organism. Impression smears were randomized, numbered, and then evaluated. The infection scores used were as follows:

Score	Basis
0	No parasites found
1	1 to 5 parasites/10 oil fields
2	ca 1 parasite/field
3	2-10 parasites/field
4	>10 but <100 parasites/field
5	>100 but <1,000 parasites/field

A score of 6 was reserved for those infections with impression smears containing >1,000 organisms/field (too numerous to count). Giemsa-stained slides were examined microscopically using a final magnification of 1008X. Methenamine silver-stained slides were examined with a final magnification of 400X.

Cysts in rat lung tissue were quantified as follows. A small portion of lung tissue from the left lobe of each rat was used to make impression smears as described above. The remainder of each lung was weighed, placed in a tube containing Hanks balanced salt solution (HBSS) (40X the lung weight) and homogenized using a Biinkman model tissue homogenizer. Two µ1 samples of the homogenized lung samples (1:4 dilution in HBSS) were placed in wells of teflon-coated, 12-well slides, stained with methenamine silver, and the number of cysts were scored as described above for the impression smears.

The activity and efficacy of two preferred N-acylcyclohexapeptides in the test animals is presented below. The compound of the formula 1 wherein R'=R"= methyl, R_1 is hydrogen and R_2 is 4[(4-phenylethynyl)phenyl]benzoyl when administered as an aerosol solution at a concentration of 5 mg/ml for one hour, twice weekly for 5 weeks resulted in 90% reduction in P. carinii cysts in the lungs. When given orally at 10 mg/kg, bid for 3 weeks, the number of cysts in the lungs was reduced by >99% when compared with infected vehicle controls.

When the preferred N-acylcyclicpeptides were administered orally and by intraperitoneal injection the compound was effective in clearing P. carinii cysts from the lungs of heavily infected rats. For example, when the

compound was administered at 10 or 40 mg/kg, bid for 4, 8 or 12 days, the number of identifiable cysts in the lungs of heavily infected rats was reduced by >99%. Similar efficacy was observed when the compound was administered i.p. at 1 mg/kg.

When tested orally for prophylactic activity, the preferred compound exhibited >99% cyst reduction in one of two studies when infected animals were dosed at 1 mg/kg and when given higher doses of 5 or 4 mg/kg.

Another preferred compound of the invention represented by the formula 1 wherein R'=R"= methyl, R_1 is hydrogen and R_2 is 4-[4-[2-(4-cyclohexylpiperidino)ethoxy]phenyl]benzoyl as the hydrochloride salt was also effective in the treatment of PCP. Aerosol prophylaxis (two 60-minute treatments twice a week for 5 weeks) was highly effective. in preventing PCP in the infected immune suppressed rats. Aerosol therapy with 5, 10, 25, or 50 mg/ml of aerosolized solution reduced the number of cysts in the lungs by >99% when compared to controls. Similar results were obtained by i.p. dosage.

The following examples of compounds of the invention and the manner of their preparation further describe the present invention.

N-Acylation of Cyclohexpeptide Nuclei

The preparation of the derivatives of the A30912A nucleus was accomplished by the following general procedure, with Table 27 listing these derivatives.

The A30912A nucleus and the 2,4,5-trichlorophenol ester are dissolved in dimethylformamide (25-50 ml) and stirred for 17-65 hours at room temperature. The solvent is removed *in vacuo* and the residue is slurried in ether and collected by filtration. The solid product is washed with methylene chloride and then dissolved in either methanol or acetonitrile/water (1:1 v/v). This solution is injected on a Waters 600E semi-preparative chromatography system using a Rainin Dynamax-60A C_{18} reverse-phase column. The column is eluted beginning with 20-40% aqueous acetonitrile and 0.5% monobasic ammonium phosphate (w/v) (monitored by UV at 230 nm and at a flow rate of 20 ml/min) until the unreacted A30912A nucleus is eluted and then deleting the buffer and eluting the product peak in aqueous acetonitrile. The fraction containing the product is evaporated *in vacuo* or lyophilized to provide the pure compound. The product may be analyzed by the same HPLC instrument using a Waters C_{18} Micro Bondapak column and eluting with 40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v) at a 2 ml/min flow rate and monitoring the UV at 230 nm. The products may also be analyzed by fast atom bombardment mass spectrometry (FABMS). (In the compounds used, R'=R"=R'"=CH_3, R=OH, R^Y=OH, R_1=H, R_7=OH, and R_2 is as defined).

TABLE 27

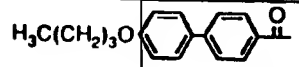
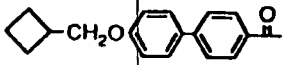
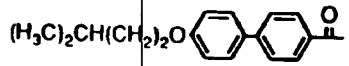
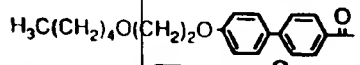
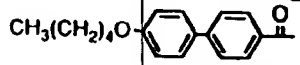
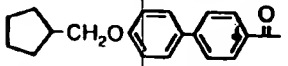
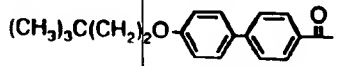
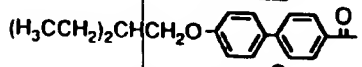
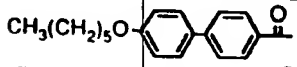
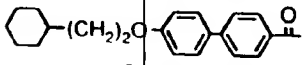
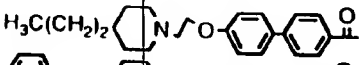
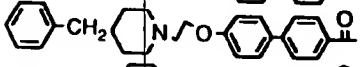
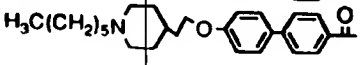
R_2	Ester Reactant (mg)	A30912A Nucleus (g)	Product (mg)	FABMS	HPLC Retention (min)
	561	1.0	235	1072*	4.08
	576	1.0	294	1062*	4.46
	579	1.0	355	1086*	5.75
	634	1.0	359	1130*	5.79
	289	0.5	81	1083*	6.08
	594	1.0	295	1098*	6.44
	596	1.0	270	1100*	8.15
	596	1.0	359	1100*	9.13
	596	1.0	301	1100*	10.24
	629	1.0	180	1104**	
	683	1.0	384	1147**	1.92
	1490	2.0	116	1195**	2.06
	1000	1.2	194	1190*+	2.41

TABLE 27 continued

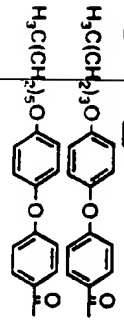
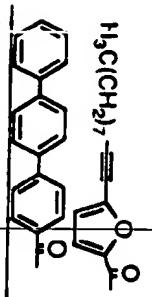
R_2	Ester Reactant (mg)	A30912A Nucleus (g)	Product (mg)	FABMS	HPLC Retention (min)
	734	0.9	303	1202*	2.21
	810	1.0	230	1187**	2.52
	750	1.0	126	1201**	3.50
	596	1.0	190	1078**	6.30
	571	1.0	295	1058**	7.91
	287	0.5	110	1082*	4.52
	593	1.0	307	1096*	7.28
	313	0.5	104	1124*	19.04
	579	1.0	293	1086*	6.14
	511	1.0	322	1032*	5.10
	514	1.0	287	1034*	6.14
	546	1.0	285	1060*	12.48
	501	1.0	218	1002**	2.53
	291	0.5	98	1088*	3.96
	616	1.0	341	1116*	11.56

TABLE 27 continued

R2	Ester Reactant (mg)	A30912A Nucleus (g)	Product (mg)	FABMS	HPLC Retention (min)
	534	1.0	215	1050***	7.59
	566	1.0	81	1054**	3.89

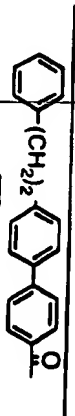
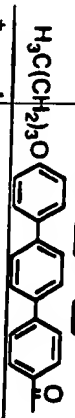
* (m-1)+[Na]+; ** (m+1); *** m+[Na]+

Compounds such as those listed in Table 27 could be further modified at the phenolic hydroxy to provide R7 = -OPO_3HNa as shown in Table 28. The procedure is as follows:

The lipopeptide (1 equivalent) and tetrabenzylpyrophosphate (2 equivalents) were dissolved in dimethylformamide which had been dried over 13X molecular sieves. Lithium hydroxide monohydrate (5 equivalents) was added and th stirred soluti n was monitored by HPLC. Aft r 0.5 hr and 1 hr m re lithium hydroxide (5 equivalents) was added. Betwe n 1 and 2 hrs. th reacti n was quenched with glacial ac tic acid, th solv nt removed under vacuum, and th r sidu purified ver a semi-pr parativ C18 rev rse- phas column using an aqu us acetonitrile eluent. Th purified product was dissolv d in (1/1) ac tic acid/water with sodium acetate (1 quival nt) and 10% Pd/C catalyst. Th solution was placed und r an atmospher f hydrogen gas and

stirr d for 1 hr. After filtering to remov the catalyst, the solution was ly philized t provide th pure final product. The purity was assessed by analytical HPLC and the product was analyz d by fast atom bombardment mass spectrometry (FABMS).

TABLE 28

R_2	Start. Mat. R_7	Wt. (mg)	Prod. R_7	Wt. (mg)	FABMS
	-OH	500	-OPO_3HNa	140	1184
$H_3C(CH_2)_3O$ 	-OH	300	-OPO_3HNa	62	1228.4472*

* m+1

Preparation of dideoxy cycloh xapeptide

The preparation of the dideoxy compounds may be accomplish d by the following pr cedure with Table 29 listing d rivativ s.

To a suspension of a non-dideoxy cyclohexapeptide (formula (I) where R=OH and R_2 is hydrogen or acyl), in dichloromethane is added the reducing agent triethylsilane in dichloromethane. The solution is stirred and the volatile components are removed under reduced pressure and the residue triturated with diethyl ether. The compound is purified using HPLC, and the product lyophilized.

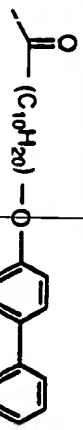
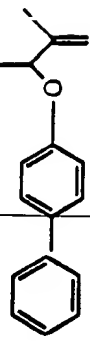
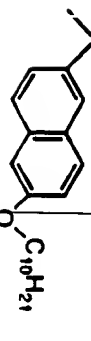
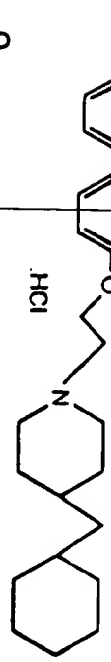
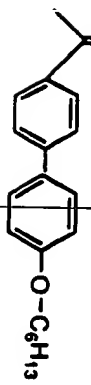
Example

Dideoxycilofungin

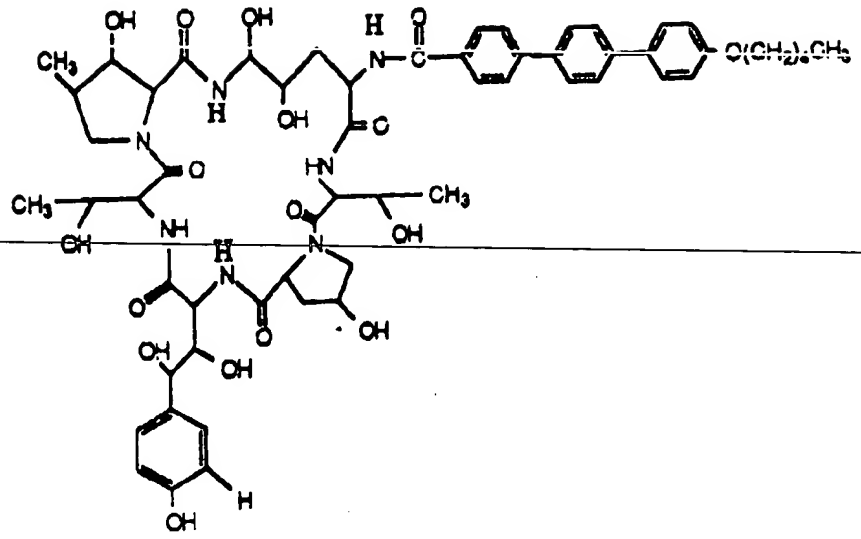
To a suspension of cilofungin (10.00 g, 9.71 mmol) in dichloromethane (100 ml) was added a solution of triethylsilane (96 m1, 602 mmol) in dichloromethane (50 ml). Trifluoroacetic acid (46.4 ml, 602 mmol) was added as a solution in dichloromethane (50 ml) over 15 minutes. The solution was stirred at room temperature for two hours. The volatile reaction components were removed under reduced pressure and the residue triturated with diethyl ether. The compound was purified by reversed phase HPLC by means of a "Prep LC/System 500" unit (Waters Associates, Inc., Milford, Mass.) using a Prep Pak 500/C_{18} Column (Waters Associates, Inc.) as the stationary phase. The column eluted with a gradient mobile phase using CH_3CN/H_2O (10:90 to 20:80 v/v) at 500 psi. The product containing fractions were pooled, evaporated under reduced pressure, and lyophilized from p-dioxane to yield dideoxycilofungin (6.66 g, 68.7%). FAB-MS: m/z calc. for $C_{49}H_{72}N_7O_{15}$, 998.5086; found, 998.512; UVλ(EtOH)nm(ε) 202.60(61012), 256.20(18569).

Table 29, indicates R_2, the amount of the cyclic hexapeptide and reagents, and yield of dideoxy compounds prepared as described above. (R'=R"=R"'=CH_3, R_1=H and R=R^Y=R_7=OH); T.E.S. = triethylsilane; TFA=trifluoroacetic acid; numbers are weights in grams).

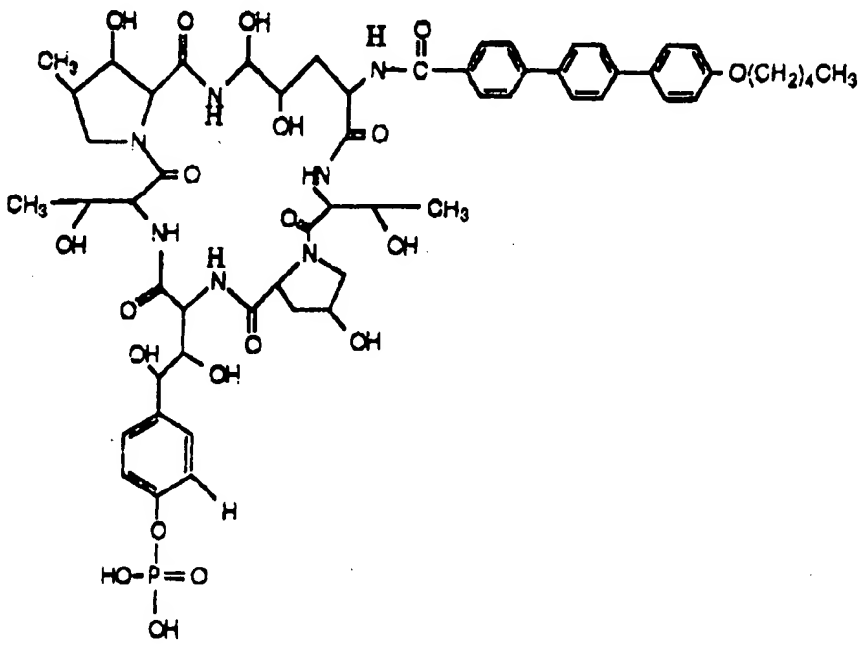
Table 29

R2	Starting Material	TES	TFA	Yield
	0.500	0.256	0.251	0.095
	0.500	2.47	2.42	0.063
	0.500	2.63	2.57	0.392
	2.00	9.49	9.72	1.47
	0.500	3.50	3.44	0.291

A compound f the formula



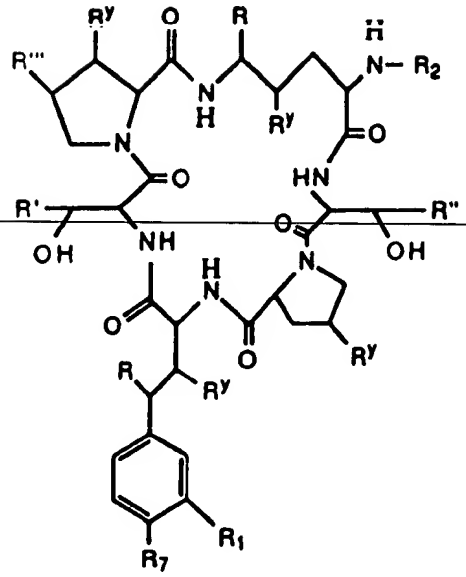
the preparation of which is discussed just prior to Table 27, can also be further modified at the phenolic hydroxy to provide R_7=-OPO_3HNa, as indicated in the two paragraphs prior to Table 28. The compound produced is as follows:



The product was analyzed by FABMS (using Lit) to give a peak at 1226.4853 (calculated for $C_{58}H_{74}N_7O_{20}PLi$=1226.4886). Also, when analyzed by HPLC using a C18 reverse-phase column and eluting with 55% aqueous acetonitrile with 0.5% acetic acid at 2 ml/min and monitoring by UV at 280 nm, the compound had a retention time of 1.72 min.

Claims

1. A compound of the formula (1):



(1)

wherein

R' is hydrogen, methyl or $NH_2C(O)CH_2$-;

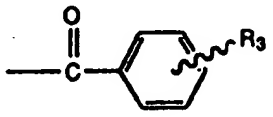
R" and R'" are independently methyl or hydrogen;

R and R^Y are independently hydroxy or hydrogen;

R_1 is hydroxy, hydrogen, or hydroxysulfonyloxy;

R_7 is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonooxy; and

I) R_2 is a substituted benzoyl group represented by the formula



wherein

A) R_3 is a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ \text{alkyl})$$

wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

B) R_3 is an unsaturated hydrocarbon group represented by the formula

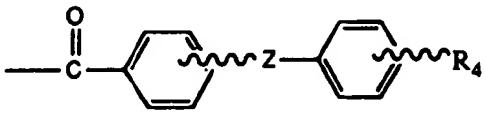
$$-Y-(C_1-C_{12}\ \text{alkyl})$$

wherein Y is -C≡C- or -CH=CH-; or

C) R_3 is a group of the formula $-O-(CH_2)_m-G$, wherein m is as defined and G is C_7-C_{10} bicycloalkyl or C_7-C_{14} tricycloalkyl; or

D) R_3 is quinolyl; or

II) R_2 is an acyl group represented by the formula



wherein

Z is -O-, -C≡C-, -CH=CH-, $-CH_2-CH_2-$, $-CH_2-$, r a carbon to carb n bond;

A) R_4 is hydrogen, C_2-C_{12} alkynyl, C_2-C_{12} substitut d alkynyl, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_1-C_{12} alkoxy, C_3-C_{12} cycloalkoxy, naphthyl, pyridyl, thienyl, b nzothienyl, qui-

nolyl or phenyl; or

B) R_4 is phenyl substituted by amino, C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_2 -C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} substitut d alkyl, C_2 -C_{12} substituted alkenyi, C_2-C_{12} substituted alkynyl, C_1 -C_{12} alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined; or

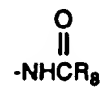
C) R_4 is phenyl substituted with C_1-C_6 alkoxy substituted by fluoro, bromo, chloro or iodo; or

D) R_4 is C_1-C_{12} alkoxy substituted with C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_2-C_{12} alkynyl, amino, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, C_1-C_{12} alkanoylamino, phenyl substituted with a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined; or

E) R_4 is C_1-C_{12} alkoxy substituted with a group of the formula



wherein R_8 is C_1-C_6 alkoxy optionally substituted with phenyl; or

F) R_4 is a group represented by the formula

$$-O-(CH_2)_{p'}-W-R_5$$

wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R_5 is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl; or

G) R_4 is a group represented by the formula

$$-Y-R_6$$

wherein Y has the same meanings defined above; and

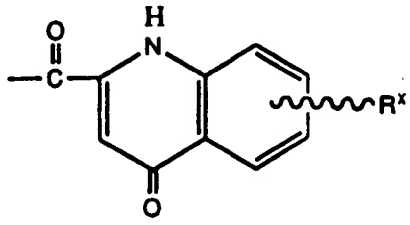
R_6 is C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl; C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, phenyl, C_3-C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, phenyl substituted by amino, C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, trifluoromethyl, -O-(CH_2)p'-W-R_6, or C_1-C_6 alkoxy substituted by fluoro, bromo, iodo or chloro; or

R_6 is a phenyl substituted by a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined above; or

III) R_2 is a group having the formula

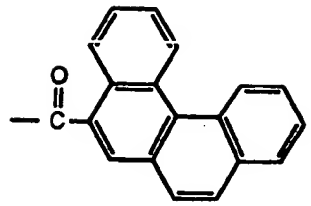


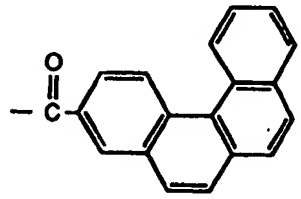
wherein R^x is C_1-C_{12} alkoxy or a polyoxa-alkyl group represented by the formula

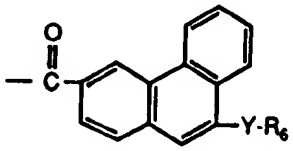
$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

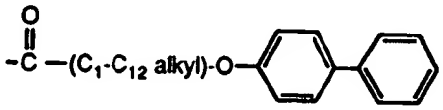
wherein m,n and p are as defined above; or

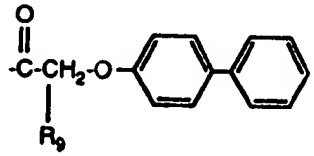
IV) R_2 is a group having the formula











wherein R_9 is phenyl, C_1-C_{12} alkyl, or C_1-C_{12} alkoxy; or

V) R_2 is naphthoyl substituted with R_4; and the pharmaceutically acceptable non-toxic salts thereof;

with the proviso that when

R' is methyl or $NH_2C(O)CH_2$-;

R" is methyl;

R‴ is methyl;

R^Y is hydroxy;

R is hydroxy; and

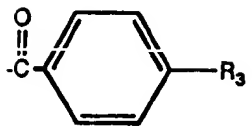
either a) or b):

a) R_1 is hydroxysulfonyloxy and R_7 is hydroxy, hydroxysulfonyloxy or phosphonooxy;

b) R_1 is hydrogen or hydroxysulfonyloxy and R_7 is hydroxysulfonyloxy or phosphonooxy;

R_2 is not

i)

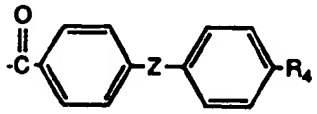


wherein R_3 is

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein p=0; nor

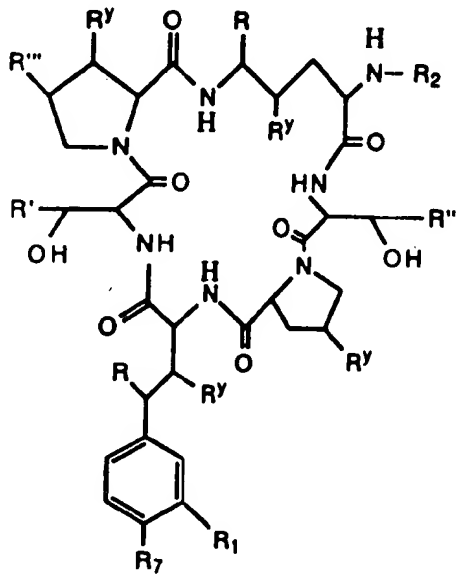
ii)



wherein Z is a carbon to carbon bond or -O- and R_4 is C_1-C_{12} alkoxy; nor

iii) naphthoyl substituted by R_4 wherein R_4 is hydrogen, phenyl, or C_1-C_{12} alkoxy.

2. A compound of the formula (1):



(1)

wherein

R' is hydrogen, methyl or $NH_2C(O)CH_2$-;

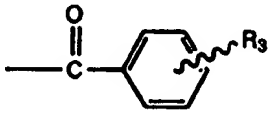
R" and R"' are independently methyl or hydrogen;

R and R^Y are independently hydroxy or hydrogen;

R_1 is hydroxy or hydrogen;

R_7 is hydroxy or hydrogen; and

I) R_2 is a substituted benzoyl group represented by the formula



wherein

A) R_3 is a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

B) R_3 is an unsaturated hydrocarbon group represented by the formula

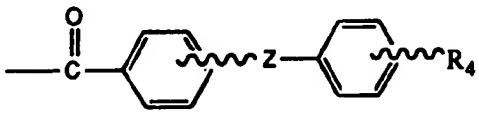
$$-Y-(C_1-C_{12}\ alkyl)$$

wherein Y is -C≡C- or -CH=CH-; or

C) R_3 is a group of the formula $-O-(CH_2)_m-G$, wherein m is as defined and G is C_7-C_{10} bicycloalkyl or C_7-C_{14} tricycloalkyl; or

D) R_3 is quinolyl; or

II) R_2 is an acyl group represented by the formula



wherein

Z is -O-, -C≡C-, -CH=CH-, $-CH_2-CH_2-$, $-CH_2-$, or a carbon to carbon bond;

A) R_4 is hydrogen, C_2-C_{12} alkynyl, C_2-C_{12} substituted alkynyl, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_1-C_{12} alkoxy, C_3-C_{12} cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

B) R_4 is phenyl substituted by amino, C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} substituted alkyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} substituted alkynyl, C_1-C_{12} alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined; or

C) R_4 is phenyl substituted with C_1-C_6 alkoxy substituted by fluoro, bromo, chloro or iodo; or

D) R_4 is C_1-C_{12} alkoxy substituted with C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_2-C_{12} alkynyl, amino, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, C_1-C_{12} alkanoylamino, phenyl substituted with a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined; or

E) R_4 is C_1-C_{12} alkoxy substituted with a group of the formula

$$-NHC(=O)R_8$$

wherein R_8 is C_1-C_6 alkoxy optionally substituted with phenyl; or

F) R_4 is a group represented by the formula

$$-O-(CH_2)_{p'}-W-R_5$$

wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R_5 is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl; or

G) R_4 is a group represented by the formula

$$-Y-R_6$$

wherein Y has the same meanings defined above; and

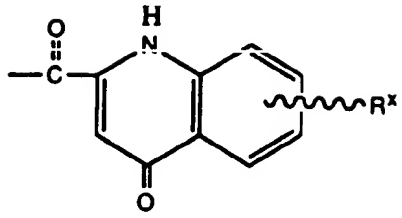
R_6 is C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl; C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, phenyl, C_3-C_{12} cycloalkenyl, naphthyl, benzothiazolyl, thienyl, phenyl substituted by amino, C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, trifluoromethyl, $-O-(CH_2)p'-W-R_5$, or C_1-C_6 alkoxy substituted by fluoro, bromo, iodo or chloro; or

R_6 is a phenyl substituted by a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

wherein m,n and p are as defined above; or

III) R_2 is a group having the formula

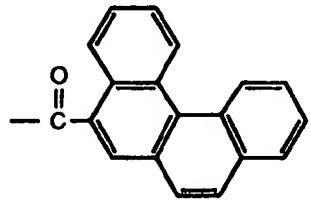


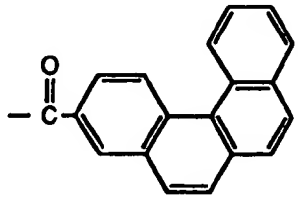
wherein R^x is C_1-C_{12} alkoxy or a polyoxa-alkyl group represented by the formula

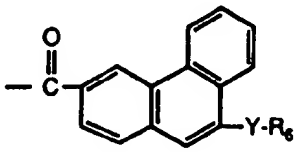
$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ alkyl)$$

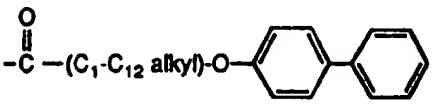
wherein m,n and p are as defined above; or

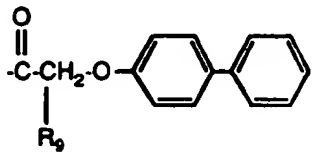
IV) R_2 is a group having the formula









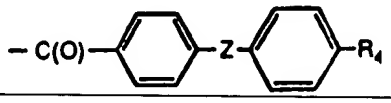


wherein R_9 is phenyl, C_1-C_{12} alkyl, or C_1-C_{12} alkoxy; or

V) R_2 is naphthoyl substituted with R_4; and the pharmaceutically acceptabl non-toxic salts th reof.

3. A compound as recited in Claims 1 or 2 wh rein R', R" and R‴ are methyl, R_1 is hydrogen, and R_7 and R^Y are OH.

4. A compound as r cit d in Claims 1 or 2 wherein R_2 is of the formula



wherein Z is a carbon to carbon bond; and

R_4 is C_1-C_{12} alkoxy, C_3-C_7 cycloalkoxy, C_1-C_6 alkoxy substituted by C_3-C_7 cycloalkyl; or

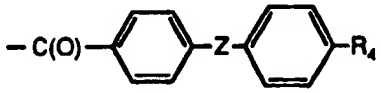
R_4 is phenyl substituted by C_1-C_{12} alkoxy or phenyl substituted with a polyoxa-alkyl group of the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]P-O-(C_1-C_{12}\ alkyl);\ or$$

R_4 is a group of the formula -Y-R_6, wherein Y is an acetylenic bond and R_6 is C_1-C_6 alkyl, phenyl, or phenyl substituted with a polyoxa-alkyl group of the formula

$$-O-(CH_2)_m-[O-(CH_2)n]P-O-(C_1-C_{12}\ alkyl).$$

5. A compound as recited in claims 1 or 2 wherein R_2 is of the formula

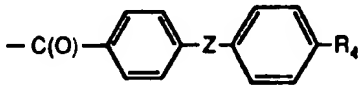


wherein Z is -C≡C- ; and

R_4 is phenyl substituted by C_1-C_{12} alkoxy or phenyl substituted with a polyoxa-alkyl group of the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]P-O-(C_1-C_{12}\ alkyl)$$

6. A compound as recited in Claims 1 or 2 wherein R_2 is of the formula



wherein Z is a carbon to carbon bond and R_4 is a group of the formula

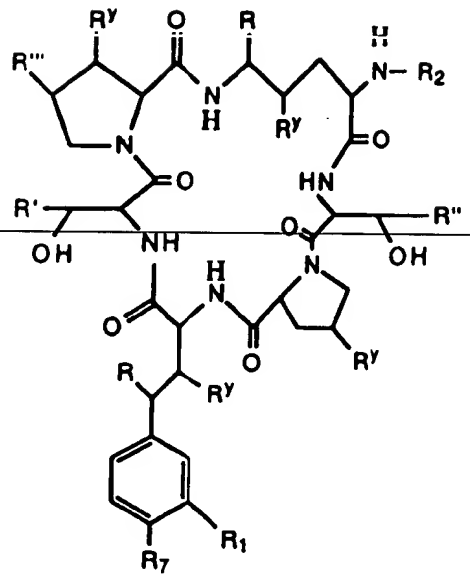
$$-O-(CH_2)_p-W-R_5$$

wherein W is a piperidine group.

7. A compound as recited in Claims 1 or 2 wherein R is hydrogen.

8. A compound as recited in claims 1 or 2 wherein R_2 is 4-(4-n-hexyloxyphenyl)benzoyl,4-(4-n-heptyloxyphenyl)benzoyl, 4-(4-n-octyloxyphenyl)benzoyl, 4-[4-(3,3-dimethylbutoxy)phenyl]benzoyl, 4-[4-(2-cyclopentylethoxy)phenyl]benzoyl, 4-[4-(2-cyclohexyloxyethoxy)phenyl]benzoyl, 4-[4-(phenylethynyl)phenyl]benzoyl, 4-[4-(n-butylethynyl)phenyl]benzoyl, or 4-[4-[2-(4-cyclohexylpiperidino)ethoxy]phenyl]benzoyl.

9. A compound of the formula (1):



(1)

wherein

R' is hydrogen, methyl or $NH_2C(O)CH_2$-;

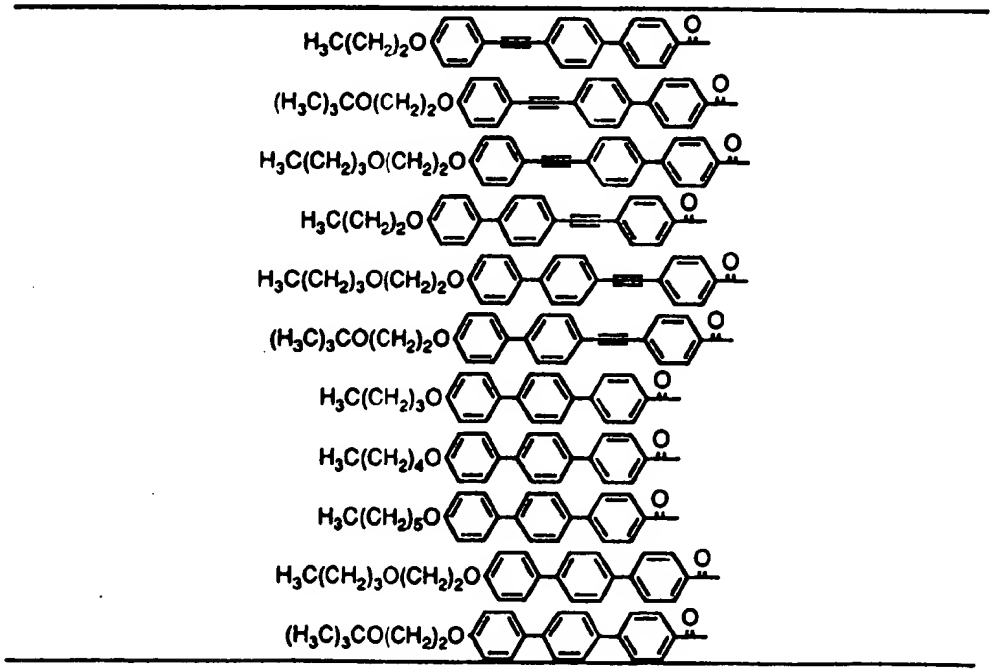
R" and R‴ are independently methyl or hydrogen;

R and R^y are independently hydroxy or hydrogen;

R_1 is hydroxy, hydrogen, or hydroxysulfonyloxy;

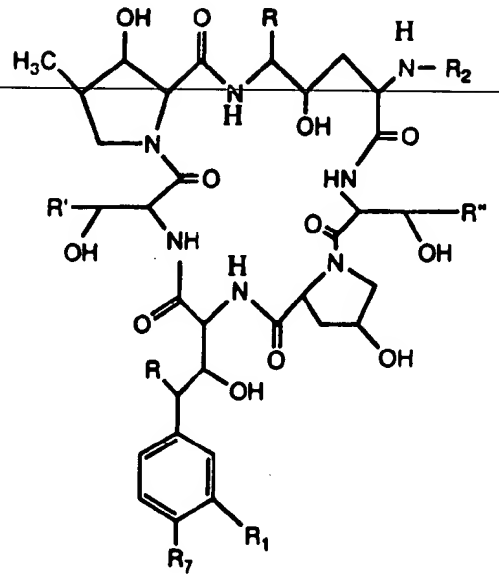
R_7 is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonooxy; and

I) R_2 is a group of the formula



R', R" and R‴ are methyl, R_1 is hydrogen and R_7 and R^Y are hydroxy and pharmaceutically acceptable salts thereof.

10. A compound of the formula (1):



(1)

wherein R' is hydrogen, methyl or $NH_2C(O)CH_2$-;

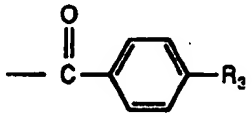
R" is methyl or hydrogen;

R is hydroxy or hydrogen;

R_1 is hydroxy, hydrogen, or hydroxysulfonyloxy;

R_7 is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonooxy;

R_2 is a substituted benzoyl group represented by the formula



wherein R_3 is a polyoxa-alkyl group represented by the formula

$$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}\ \text{alkyl})$$

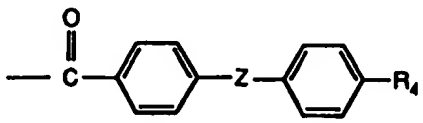
wherein m and n are integers of from 2 to 4, and p is 0 or 1; or R_3 is an unsaturated hydrocarbon group represented by the formula

$$-Y-(C_1-C_{12}\ \text{alkyl})$$

wherein Y is -C≡C- or -CH=CH-;

or R_3 is a group of the formula $-O-(CH_2)_m-G$, wherein m is as defined and G is C_7-C_{10} bicycloalkyl or C_7-C_{14} tricycloalkyl;

or R_2 is an acyl group represented by the formula



wher in Z is -O-, -C≡C-, -CH=CH-, $-CH_2-CH_2-$, or a carbon to carb n bond;

R_4 is hydrogen, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, phenyl, ph nyl substitut d by amino, C_1-C_{12} alkylthi , halogen, C_1-C_{12} alkyl, C_1-C_{12} alk xy, trifluorom thyl, phenyl, or C_1-C_6 alkoxy substituted by fluoro, bromo, chloro or iodo;

or R_4 is C_1-C_{12} alkoxy, C_3-C_{12} cycloalkoxy, C_1-C_{12} alkoxy substituted by C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, amino, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, C_1-C_{12} alkanoylamino or a group of the formula

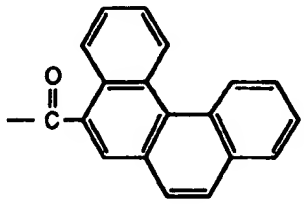
wherein R_8 is C_1-C_6 alkoxy optionally substituted with phenyl; or R_4 is a group represented by the formula

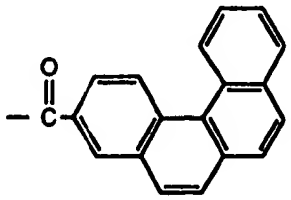
$$-O-(CH_2)_p-W-R_5$$

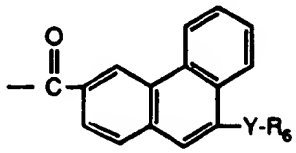
wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R_5 is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl;

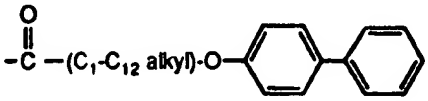
or R_4 is a group represented by the formula -Y-R_6 wherein Y has the same meanings defined above and R_6 is C_1-C_{12} alkyl, C_1-C_{12} alkyl substituted by phenyl; C_3-C_{12} cycloalkyl, phenyl, C_3-C_{12} cycloalkenyl, naphthyl, benzthiazol-2-yl, or phenyl substituted by amino, C_1-C_{12} alkylthio, halogen, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, C_1-C_{12} alkoxy, trifluoromethyl, -O-(CH_2)p'-W-R_5, or C_1-C_6 alkoxy substituted by fluoro, bromo, iodo or chloro; or

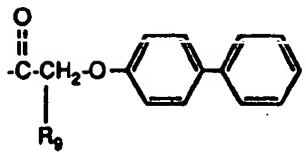
R_2 is a group selected from











wherein R_9 is phenyl, C_1-C_{12} alkyl, or C_1-C_{12} alkoxy; or

~~R_2 is naphthoyl substituted with R_4; and the pharmaceutically acceptable non-toxic salts thereof;~~

with the proviso that when

R' is methyl or $NH_2C(O)CH_2$-;

R" is methyl;

R is hydroxy; and

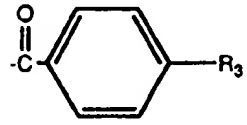
either

a) R_1 is hydroxysulfonyloxy and R_7 is hydroxy, hydroxysulfonyloxy or phosphonooxy; or

b) R_1 is hydrogen or hydroxysulfonyloxy and R_7 is hydroxysulfonyloxy or phosphonooxy;

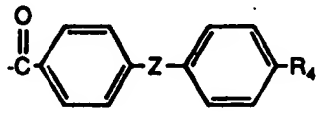
R_2 is not

i)



wherein R_3 is -O-$(CH_2)_m$-$[O$-$(CH_2)_n]_p$-O-(C_1-C_{12} alkyl) wherein p=O; nor

ii)



wherein Z is a carbon to carbon bond or -O- and R_4 is C_1-C_{12} alkoxy; nor

iii) naphthoyl substituted by R_4 wherein R_4 is hydrogen, phenyl, or C_1-C_{12} alkoxy.

11. A compound as recited in claim 10 wherein R_1 is not hydroxysulfonyloxy and R_7 is not hydroxysulfonyloxy or phosphonoxy.

12. A compound of any of claims 1-11 for use in inhibiting parasitic activity.

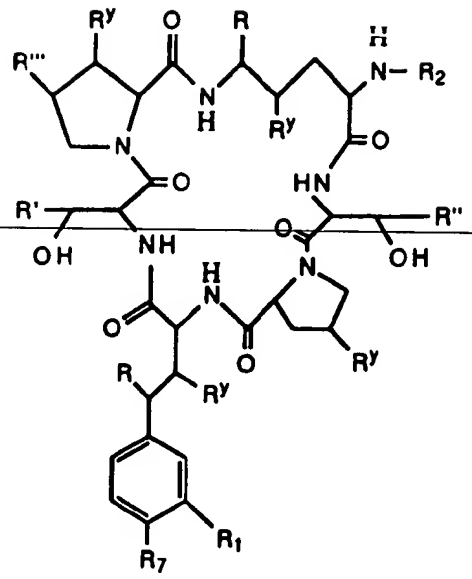
13. A compound of claims 1-11 for use in inhibiting fungal activity.

14. A compound of any of claims 1-11 for use in inhibiting the growth of organisms responsible for opportunistic infections in immunosuppressed individuals.

15. A compound of claims 1-11 for use in inhibiting the growth of Pneumocystis carinii.

16. A pharmaceutical formulation comprising a compound of any of Claims 1-11 and a suitable pharmaceutical carrier.

17. A process for the preparation of a compound of the formula (1):



(1)

wherein R' is hydrogen, methyl or $NH_2C(O)CH_2$-;

R" and R"' is methyl or hydrogen;

R is hydrogen;

R^y is hydroxy or hydrogen,

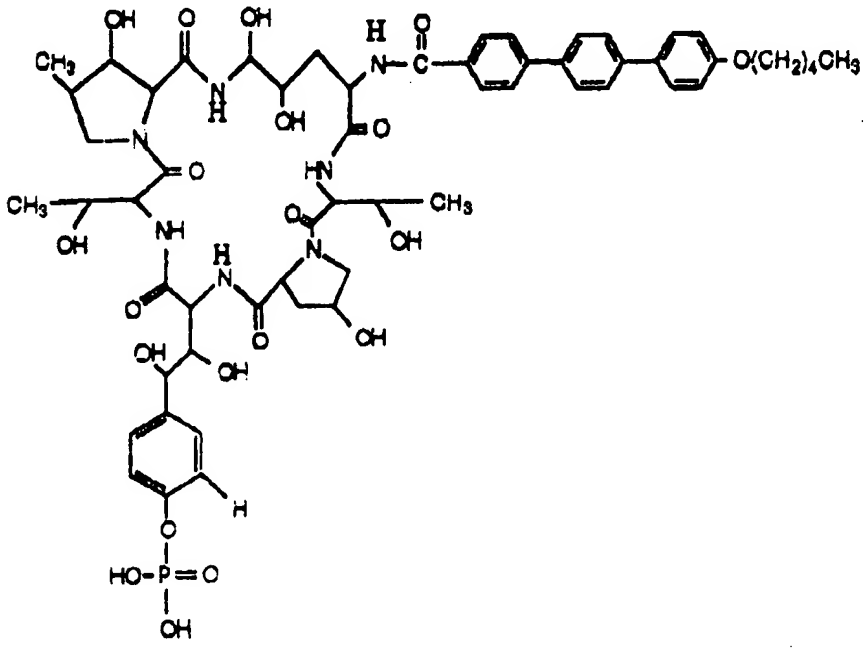
R_1 is hydroxy, or hydrogen;

R_7 is hydroxy, or hydrogen; and

R_2 is hydrogen or acyl;

comprising the step of subjecting a compound of formula (I) wherein R=OH, to a strong acid in the presence of a reducing agent, in a suitable solvent.

18. A compound of the formula



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93302064.6

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP - A - 0 448 343 (MERCK & CO. INC.) * Claims 1-7 * --	1-18	C 07 K 7/56 A 61 K 37/02
A	EP - A - 0 448 354 (MERCK & CO. INC.) * Claims 1-7 * --	1-18	
A	EP - A - 0 447 186 (MERCK & CO. INC.) * Claims 1-7 * ----	1-18	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 K 7/00
A 61 K 37/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	28-05-1993	SCHARF

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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